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MEDIASTINAL TUMOR IN ACUTE LEUKEMIA

A CLINICAL AND ROENTGENOLOGIC STUDY

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The purpose of this paper is to report a group of nine cases of acute leukemia with large mediastinal tumors or infiltrations, and the results of roentgen therapy on this condition. While the occasional presence of such tumor masses in acute leukemia has been recognized, the lack of any but casual reference to them in standard texts indicates that they are considered rare. It is becoming increasingly evident, however, that a definite proportion of patients with acute leukemia have mediastinal masses which tend to give characteristic symptoms of pressure. These tumors may precede the typical blood changes, and, in my observation, they have been the most common form of massive mediastinal enlargement in children.

Localized tumor masses composed of round sarcoma-like cells have at times been observed at necropsy in patients dying of acute leukemia. These have been noted most frequently in the anterior mediastinum and have usually been considered of thymic origin, but have occurred less often in other locations, as, for example, the subcutaneous tissues, skin, bones and serous membranes. Sternberg, in 1905, designated the group of cases with localized lymphoid tumors and a leukemic blood picture as "leukosarcoma," because of his belief that they represented a true neoplastic tumor, and his view and term have met with rather wide acceptance. Such observers, however, as Naegeli and Fraenkel have felt that such tumor masses are only a part of the leukemia, and consider that they are comparable to the tumors found not infrequently in the cervical and other lymph nodes. Similar mediastinal tumors in patients without blood changes or other signs of acute leukemia have been called lymphosarcomas or thymomas. Most of these cannot be differentiated from leukemic tumors even by microscopic sections.

Since no one has attempted to collect the observed cases of such mediastinal leukemic tumors, the frequency of their occurrence has been hard to estimate. Until recently the recorded observations have been made entirely on cases at necropsy, and the tumors have not always

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been recognized clinically, so that instances of the condition without necropsy may have been missed. That these mediastinal masses have been observed more frequently than is usually appreciated is indicated by the fact that seventy-four such cases have been collected in the accompanying table. All of those cited have been accompanied by sufficient data to show that they are examples of the same condition, although the authors reporting them have variously interpreted their character. Only the age, sex and highest leukocyte count in each case have been tabulated, together with the duration of illness and size of the mediastinal tumor when available. On reviewing the individual clinical and pathologic reports, it is noticeable that the only feature by which they differ from a similar series of cases of acute leukemia is by the presence of the mediastinal tumor. The clinical manifestations, the blood picture, the eventual glandular and splenic enlargement, the extensive infiltration of the bone marrow, liver and kidneys by non-granular mononuclear cells are identical whether or not a mediastinal mass is present. Only by the physical signs of a solid substernal tumor, or, in certain instances, by the symptoms of mechanical obstruction to respiration, are the patients with mediastinal involvement recognized clinically. Certain other features of the condition will be commented on after describing the cases to be reported.

During the past few years several writers have recognized the mediastinal mass, especially by the use of the roentgen rays, and have treated it by irradiation. In certain of these patients the blood changes of acute leukemia have appeared some time after the appearance of the mediastinal tumor in a manner quite similar to that observed in several of the children whose cases are here reported. Brief summaries of these cases will be given, because the effect of irradiation is a feature of special interest.

Webster (no. 51) reported the case of a man 28 years old, who for four months had had cervical enlargement, cough, dysphagia and orthopnea. There were dilated veins of the neck and face, palpable firm cervical and axillary lymph nodes, liver and spleen, retromanubrial dulness and a large mass located in the mediastinum with a roentgenogram. The leukocytes were 3,900, with 60 per cent polymorphonuclears. During the following two weeks, the symptoms of pressure became accentuated and anisocoria developed, more marked on the right, but the blood showed no leukocytosis or abnormal cells. A lymph gland excised from the neck showed lymphosarcoma. Irradiation with the roentgen rays was then given over the chest for one-half hour daily during the next ten days. This resulted in subjective improvement with reduction in dyspnea and cough, but was discontinued because ecchymoses developed abundantly and rapidly, and the leukocytes increased to 31,000. A week later they were 87,400, practically all lymphocytes. The hemorrhages continued, fever developed, the lymph

Reported Cases of Mediastinal Tumor in Acute Leukemia

No.	Reported by	Year	Age	Sex	Leukocytes	Size of Tumor	Duration
1	Ehrlich	1862	20	M	1:20 r.b.c.	20 × 4.5 × 1 cm.	1½ mo.
2	Taylor	1874	12	M	1:10 r.b.c.	Large; 2.5 cm. thick	11 wk.
3	Smith	1874	31	M	1:1 r.b.c.	Large	5 mo.
4	Kelsch	1875	26	M	1:3 r.b.c.	Enormous; 2-3 cm. thick	7 wk.
5	Gowans	1876	25	M	1:2 r.b.c.	Large	5 mo.
6	Morison	1877	7	F	Increased	Very large	1½ mo.
7	Turner	1878	15	M	1:12 r.b.c.	Large	4 mo.
8	Mosler	1879	9	M	1:10 r.b.c.	14 × 8 cm.	2 wk.
9	Gaucher	1881	38	M	1:20 r.b.c.	"Orange"	9 wk.
10	Ebstein	1889	23	M	163,650	Large	3 wk.
11	Oberastzow	1890	17	M	1:7 r.b.c.	9 × 9 × 5 cm.	3 mo.
12	Grawitz	1890	22	M	Increased	Very large	1 wk.
13	Dreschfeld	1891	23	M	1:30 r.b.c.	Large	6 wk.
14	Guttmann	1891	10	M	1:1.4 r.b.c.	9 × 7 × 3.75 cm.	1 mo.
15	Nobl	1892	30	F	1:50 r.b.c.	.....	3 wk.
16	Palma	1892	18	M	372,000	Very large	5 mo.
17	Hindenburg	1895	5	M	700,000	8.5 × 8.4 cm.	2½ mo.
18	Seelig	1895	11	M	1:5.4 r.b.c.	Large	1½ mo.
19	Litten	1895	20	M	1:40 r.b.c.	Large	
20	Reimann	1899	9	F	350,000	Large	6 wk.
21	Sérard	1900	5	F	54,250	8 × 6 cm. (150 Gm.)	2 wk.+
22	Sérard	1900	16	M	124,000	60 Gm.	2 mo.
23	Rocaz	1902	4	M	245,000	10 × 12 × 4 cm. (200 Gm.)	1 mo.
24	Kelly	1903	11	M	378,000	5 × 8 × 2 cm.	3 mo.
25	Sternberg	1904	14	M	800,000	8 cm. wide	3 wk.
26	Coenen	1904	6	M	Frank leukemia	15 × 13 × 5.5 cm.	4 wk.
27	Pfannkuch	1904	23	M	1,000,000	Large	2 mo.
28	Heubner	1904	2	?	92,000	Large	1 mo.
29	McCrae	1905	20	M	12,000	13 × 4 cm.	2 mo.
30	Ogawa	1905	17	M	108,000	Large	
31	Brandenberg	1906	6	M	Exceeded r.b.c.	18 × 9.5 cm.	1 mo.
32	Lehndorff	1906	5	F	103,000	Large	2 mo.
33	Leader	1906	11	M	21,500	12.7 × 8.3 cm. (200 Gm.)	4 mo.
34	Fabian et al	1907	8	?	74,000	11.5 × 9 cm.	7 wk.
35	Fabian et al	1907	28	?	212,000	8 × 8 × 2 cm. (40 Gm.)	1 mo.
36	Goldschmidt	1907	16	F	Much increased	150 Gm.	1 mo.
37	Mager	1909	21	M	810,000	Large	1 mo.
38	Paltauf	1912	24	M	Enormous increase	Large	3 wk
39	O'Kelly	1914	19	M	295,000	"Closed fist"	1½ mo.
40	Sternberg	1916	19	M	Much increased	"Mächtig"	1 mo.
41	Sternberg	1916	16	F	Increased	22 × 13 × 6 cm.	1 mo.
42	Major	1918	42	F	41,000	10 × 7 × 7 cm. (189 Gm.)	2 mo.
43	Weber	1919	18	M	176,000	Large	2½ mo.
44	Weber	1919	7	M	103,000	Large	2 mo.
45	Weber	1919	5	F	60,000	Large	
46	Harrison and McKelvey	1920	29	M	210,000	"Coconut"	4 mo.
47	Wagner	1920	5	M	360,000	Large	2 mo.
48	Janeway	1920	8	M	143,000	6 × 8 cm.	4 mo.
49	Webster	1921	23	M	33,000	10 × 4 cm.	7½ mo.
50	Webster	1921	7	M	230,500	18 × 15 × 9.5 cm.	7 mo.
51	Webster	1921	28	M	87,400	Large	5½ mo.
52	Webster	1921	12	F	81,000	Large	5 wk.
53	deJong and Louet	1924	17	F	258,000	22 × 12 cm.	1 mo.
54	DeSautelle and Wood	1925	23	M	122,200	11.5 × 10 × 3 cm. (200 Gm.)	1½ mo.
55	Fernández et al	1925	6	M	130,000	"Fetal head"	2 mo.
56	Friedlander and Foot	1925	38	F	320,000	10 × 6 × 5.5 cm.	1 mo.
57	McWeeney	1925	9	M	783,000	Enormous	9 wk.
58	Evans and Leucutia	1926	23	M	144,000	Large in roentgenogram	6 mo.
59	Evans and Leucutia	1926	15	M	400,000	Large in roentgenogram	3 mo.
60	Thorpe	1927	6	M	151,000	Large in roentgenogram	3 mo.
61	Borchardt	1927	43	M	100,800	Large	6 wk.
62	Young and Spalding	1928	8	M	1,016,000	Very large	1½ mo.
63	Hensel	1928	13	M	832,000	Large in roentgenogram	5 mo.
64	Landau	1929	5	M	56,000	Large in roentgenogram	4½ mo.
65	Nicholson	1929	26	M	270,000	Large	3½ mo.
66	Nicholson	1929	40	M	42,500	Large	3½ mo.
67	Gorlitzer	1930	26	M	32,400	Large	2 mo.
68	deLavergne et al	1930	20	M	41,000	Large	7 wk.
69	Weil et al	1930	19	M	460,000	Enormous	3 wk.
70	Margolis	1930	5	M	8,000	50 Gm.	
71	Margolis	1930	2	M	32,800	215 Gm.	
72	Margolis	1930	8	M	232,000	255 Gm.	
73	Margolis	1930	23	M	297,000	470 Gm.	
74	Zohman	1931	48	M	36,000	Large in roentgenogram	2 mo.

nodes became enlarged, and 200 cc. of bloody fluid was aspirated from the left pleural cavity. Death occurred three weeks after the last irradiation. At necropsy the mediastinal tumor was large and composed of lymphocytes, with a like infiltration of the spleen, liver, kidneys and bone marrow.

Evans and Leucutia described two patients with mediastinal tumors treated by irradiation, with development of acute lymphatic leukemia later. The first (no. 58) was that of a man 23 years old who had marked respiratory distress and cyanosis from a large mediastinal mass pressing on the trachea and visible in a roentgenogram. The leukocytes were 14,100, with 72 per cent polymorphonuclears and no abnormal cells. Roentgen therapy caused rapid improvement, and within ten days the mediastinal mass had entirely disappeared. Three months later nodules were noted in the scalp, and these also disappeared after irradiation. The blood count at this time was normal, but a month or so later cutaneous hemorrhages developed, and the blood count was 144,000, with a high percentage of lymphocytes. The patient died about six months after the first symptoms of mediastinal tumor were noted. At necropsy no thoracic tumor remained, but a much enlarged spleen, marked hyperplasia of the bone marrow and a nodule of infiltrating lymphocytic cells in one auricle were described. The anatomic diagnosis was lymphosarcoma. The second case (no. 59) was quite similar and was that of a 15 year old boy, with cyanosis, difficulty in breathing and a large mediastinal shadow. Examination of the blood showed 12,500 leukocytes, with 66 per cent polymorphonuclears. After deep roentgen therapy the symptoms and the retrosternal mass disappeared within ten days. Three months later weakness, pain in the legs and a tumor in the left testicle developed. The blood showed a rapidly progressing lymphatic leukemia with the final count over 400,000. No necropsy was obtained. The authors considered these cases to be lymphosarcoma and expressed the opinion that metastatic extension of the neoplasm to the bone marrow produced acute leukemia.

Young and Spalding's patient (no. 62) was an 8 year old boy who suffered from a sudden severe dyspnea due to a mediastinal tumor and left pleural exudate. The leukocytes were 22,000, with 76 per cent polymorphonuclears. Irradiation was followed by marked relief from the symptoms, but after two weeks the dyspnea again became extreme, and the leukocytes rose to 1,016,000 with 93 per cent lymphocytes. Necropsy, at which only the chest was examined, showed a very large mediastinal mass diagnosed lymphosarcoma.

Hensel reported the case of a 13 years old boy (no. 63), with cough and dyspnea of four weeks' duration, marked retromanubrial dulness and an irregular shadow in the anterior mediastinum. The blood count was 13,000, with 58 per cent polymorphonuclears and no abnormal cells. Clinical improvement and a reduction in the size of the mediastinal

shadow followed roentgen treatment of the chest. The dyspnea returned in about six weeks, and several months later fever and hemorrhages and enlarged cervical nodes, liver and spleen developed. The blood then showed 832,000 cells, with 99 per cent mononuclears. Necropsy showed "lymphosarcoma of the thymus." Typical leukemic infiltration of the liver and kidneys was described.

Landau described a 5 year old boy (no. 64) with some dyspnea and cough. A roentgenogram showed a mediastinal shadow and left pleural exudate. The leukocytes were 13,200, with 78 per cent polymorphonuclears. The spleen was palpable, and an excised small lymph node from the axilla showed lymphosarcoma. Roentgen treatments were given, and during the next month the symptoms of respiratory distress disappeared together with the mediastinal shadow and pleural exudate, and the slightly enlarged lymph nodes and spleen became of normal size. The leukocyte count was 5,100, with 23 per cent lymphocytes. About two months after the irradiations, much enlarged cervical glands and spleen, cutaneous and intestinal hemorrhages and anemia developed. Examination of the blood then showed 56,000 leukocytes, with 87 per cent lymphocytes. Death occurred two weeks later, and at necropsy a leukemic infiltration of the parenchymatous organs, lymph nodes and bone marrow was found, but no mediastinal tumor.

It is rather striking that almost all the authors who have reported such cases have considered the condition one of a true mediastinal neoplasm of the lymphosarcoma type, and that the acute leukemia resulted in some way from the primary new growth.

The nine cases with mediastinal tumors to be reported here were part of a group of thirty-eight cases of acute leukemia in children observed at the St. Louis Children's Hospital during the past six years. This is an incidence for this group of 24 per cent with such mediastinal involvement. None of the other twenty-nine patients had any clinical evidence of mediastinal tumor. In fifteen, no mediastinal enlargement was demonstrable in roentgenograms or at necropsy, while in the remainder no roentgenograms were taken or necropsies performed. The only other figures available for comparison are from a report by Margolis, who examined the pathologic material from a number of patients with leukemia who came to necropsy at the Mayo Clinic. Of the ten children in this group who had acute leukemia of either lymphatic or aleukemic types, three were found to have large anterior mediastinal tumor masses.

The nine patients with mediastinal tumors and leukemia whose cases are herein reported were all white boys between 3 and 13 years old. The blood picture of each was typical of acute lymphatic leukemia, with a tremendous preponderance of nongranular mononuclear cells and a small percentage of granular polymorphonuclears. Only one child had no leukocytosis, although several had "aleukemic" phases while under

observation. The abnormal mononuclears varied somewhat in size, but usually a considerable number were "large lymphocytes." Oxydase stains showed no granules in the mononuclear cells, and only rarely was a myelocyte seen. All patients had anemia and thrombocytopenia in the later stages of the disease.

The character and origin of the abnormal nongranular cells present in the blood in acute leukemia is still in dispute. They have long been considered by many observers to be lymphocytes or lymphoblasts, and the common term "acute lymphatic leukemia" expresses their presumably lymphoid origin. In recent years the view that such cells originate in the bone marrow and are more closely related to myeloblasts has been gaining favor. In addition to their morphologic resemblance, their biologic relationship is indicated by the demonstration (by myself) of the similarity of the proteolytic ferment content of the acute leukemic cells and the granular myeloid cells. Reference in this paper to these leukemic cells as lymphocytes follows the usual custom to avoid confusion, although they are probably myeloblasts.

Of the nine children with mediastinal tumors, four came under observation before any changes in the blood were demonstrable, and had symptoms of severe respiratory obstruction; the remaining five had typical leukemic changes when first seen. One of the latter had marked symptoms of respiratory embarrassment, two had mild symptoms, and the other two had none.

Summaries of the records of these nine children follow:

REPORT OF CASES

CASE 1.—*History.*—R. M., a boy, aged 12 years, somewhat undernourished and moderately pale, was first seen on Aug. 7, 1925, with difficult respiration and an inspiratory stridor. He had been active and well until ten days previously, when a paroxysmal cough developed, and at times he "nearly choked to death." There were no other complaints except that he had had fever with a temperature of 102 F. once five days before admission.

Examination.—On examination the tonsils and the cervical lymph nodes were considerably enlarged, with the largest cervical gland the size of a hen's egg on the right side (fig. 1 *A*). The inguinal and axillary nodes were palpable but not visible, and none of the glands was tender. Neither the spleen nor the liver was palpable. In addition to the dyspnea there was a brassy cough at frequent intervals and well marked right parasternal dulness. A roentgenogram of the chest (fig. 2 *A*) revealed a large globular shadow apparently lying in the anterior mediastinum, since the trachea appeared in the midsternal line. Its left border was clearcut, but the right was hazy. The mass extended from the clavicle above to merge with the cardiac shadow below, obscuring the hilus on each side and reaching well out into the fields of both lungs. Biopsy of an axillary lymph node showed complete loss of normal gland architecture with a scanty stroma in which was a diffuse infiltration by nongranular mononuclear cells of the type found in lymphosarcoma and acute leukemia. There were no necrosis, inflammatory reaction or any suggestion of Hodgkin's disease. Examination of the blood showed 4,700,000 erythrocytes and 9,200 leukocytes, with 71 per cent polymorphonuclears, 17 per cent lymphocytes and 12 per cent monocytes. Platelets were abundant.

Fig. 1 (case 1).—*A*, "preleukemic" cervical glandular enlargement in a 12 year old boy; *B*, appearance five days later after roentgen therapy.

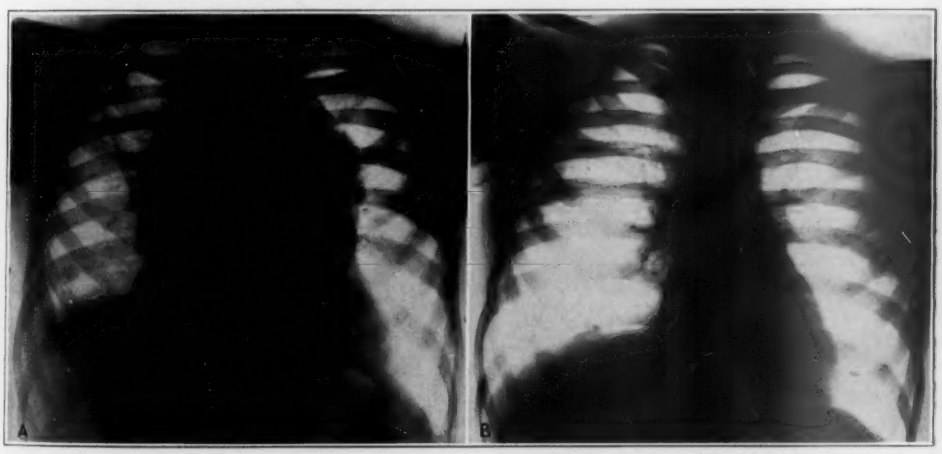

Fig. 2 (case 1).—Roentgenograms showing *A*, large mediastinal tumor producing severe symptoms of pressure, and *B*, complete disappearance of the mediastinal shadow five days later, after irradiation.

Course.—Roentgen therapy [1] was given on August 8 and 11, a total dose of six minutes over two areas. The first treatment was followed by some nausea and vomiting, but the next day respiration was less difficult, and three days after the initial irradiation the cough and dyspnea had entirely disappeared, while the cervical swelling had regressed noticeably. The second irradiation produced no symptoms. On the fifth day following the first therapy, the cervical glands were barely palpable, and the mediastinal shadow could not be seen (figs. 1 *B* and 2 *B*). The patient was discharged on August 14. At that time the leukocytes had fallen to 6,200, with 82 per cent polymorphonuclears, 11 per cent lymphocytes and 7 per cent monocytes.

Second Admission.—The boy was readmitted to the hospital on September 30, with the interval history that a circumcision had been done in another institution, and there had been so much oozing from the wound that four transfusions of blood had been required. The cervical glands had again become much enlarged, and a severe epistaxis, lasting three hours and requiring packing, had occurred the day before admission. There was no respiratory difficulty. On examination, in addition to the much enlarged firm cervical glands, the inguinal and axillary groups were bean-sized, and the liver and spleen were greatly enlarged. Petechial hemorrhages were present on the face and on the palatal and pharyngeal mucosa. The leukocyte count was 110,000, with 98 per cent lymphocytes, and the platelets were much decreased. During the following week there was little change in the patient's condition, except that the temperature rose to between 39 and 40 C. (102.2 and 104 F.). The leukocyte count remained high. The boy was removed from the hospital on October 6, and died three days later. No necropsy was done.

Case 2.—*History.*—A. M., a boy, aged 5 years, well nourished and developed, came under observation first on Nov. 19, 1928, with the history that he had had two nocturnal "choking attacks" during the previous month, stridor for the preceding week and cyanosis for two days. The cervical gands had become enlarged during the past week.

Examination.—On examination the right pupil was larger than the left; there was marked respiratory difficulty with stridor, and the tonsils and left posterior cervical glands were moderately enlarged with a walnut-sized mass in the suprasternal fossa. The other cervical nodes as well as the axillary and inguinal glands were only slightly larger than normal. The spleen and liver were palpable. Right parasternal dulness was present, and a roentgenogram on November 20 (fig. 3 *A*) showed an enormous widening of the mediastinal shadow, which had a lobulated border and extended up through the circle of both first ribs. On the left, the shadow came to within 2 cm. of the thoracic wall just above the midaxilla, but did not extend so far on the right side. An oblique view showed the shadow to be in the anterior mediastinum. The leukocyte count was 12,200, with polymorphonuclears, 61 per cent; lymphocytes, 27 per cent, and monocytes, 12 per cent. The erythrocytes numbered 3,600,000. There was no fever. Irradiation was given on November 21, 22, 23, 27 and 30, for a total of twelve minutes. After the first treatment, the dyspnea and cyanosis disappeared, and after the third the suprasternal mass and cervical enlargements were gone. A flat roentgenogram of the chest taken on November 26 (fig. 3 *B*), six days after the first treatment, showed no mediastinal shadow. The leukocytes had decreased to 5,400, but the differential count was normal.

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1. Therapy in this and the following patients was given under the direction of Dr. Sherwood Moore, as follows: kilovolts, 200; milliamperes, 30; distance, 50 cm.; portal, 20 cm.; filters, 1 mm. of copper and 1 mm. of aluminum. The chest and back were irradiated equally on alternate treatments.

Course.—For several days after the patient's discharge on December 2, his appetite was good, and he was active physically. Within three weeks the cervical lymph nodes became enlarged, and when he was readmitted on December 26, he had petechial hemorrhages on the abdomen, extremities and oral mucous membranes and clotted blood in the nose. Anisocoria was still present. The spleen was 6 cm. below the costal margin and was firm, but a roentgenogram showed no recurrence of the mediastinal mass. The boy was under observation in the hospital for a month. During the first two weeks he had fever with a temperature from 38 to 40 C. (100.4 to 104 F.) and asthenia, and seemed to be getting worse, with cervical nodes increasing in size and hemorrhages at intervals from the nose and mouth. Following several transfusions of blood, he became afebrile; no more hemorrhages occurred, and the general condition was much improved when he was discharged on Jan. 28, 1929. Clinically, the condition was rather typical of acute leukemia. The blood showed a leukopenia of from 1,000 to 3,600 during the first two weeks of this admission, with thrombocytopenia and anemia. The differential blood count, however, showed no striking decrease in polymorphonuclears, and

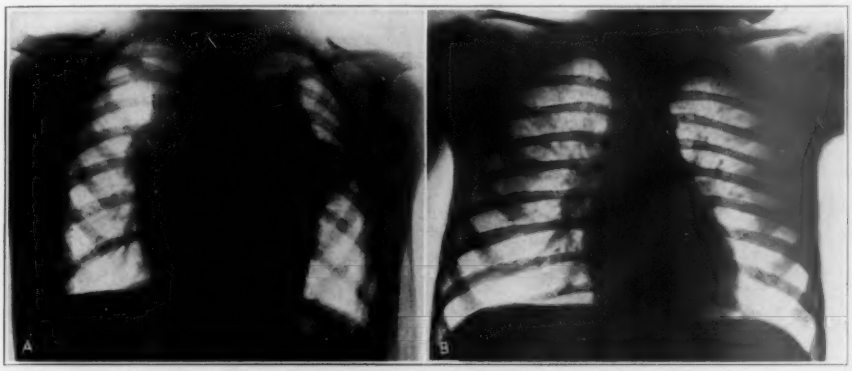

Fig. 3 (case 2).—Roentgenograms showing *A*, mediastinal tumor in a 5 year old boy with stridor and cyanosis; *B*, six days later, disappearance of mediastinal shadow after roentgen therapy.

later the count rose so that on discharge on January 28 there were 7,000 leukocytes, with 60 per cent polymorphonuclears. No definitely abnormal lymphocytes were identified.

Second Admission.—After two weeks at home the patient was readmitted on February 14, with a considérable increase in the size of the cervical nodes and spleen, ecchymoses on the trunk and extremities and fever, with a temperature of 38 C. A roentgenogram showed no recurrence of the mediastinal mass. The blood had 33,000 leukocytes, with 5 per cent polymorphonuclears and 95 per cent lymphocytes. Following irradiation to the neck and a transfusion of blood for a severe epistaxis, there was considerable symptomatic improvement and the cervical enlargements became less. A hopeless prognosis was given in spite of the temporary improvement, and the patient was discharged. While being taken to the train, the taxicab in which he was riding was struck by a trolley car and he was killed.

Case 3.—*History.*—W. S., a boy aged 5 years, who had always been active and strong, complained of cough, edema of the face and dilated prominent veins of the chest and neck developing about April 15, 1930. The symptoms became more

severe, and when the patient was first seen by Dr. Adrien Bleyer a large mediastinal tumor was shown by roentgenogram (fig. 4) taken on April 30. The shadow extended from the organs of the neck down over the heart and well out into the fields of both lungs. On the right the border was hazy, while on the left it was wavy but clearcut. The blood count was normal, and there was no enlargement of the superficial lymph nodes or spleen. Following roentgen therapy on April 25, May 2 and May 9 there was complete disappearance of the edema, cyanosis and cough, but no change was seen in the extent of the mediastinal shadow on May 16. The symptoms of compression gradually recurred, so that the boy was unable to sleep, and when admitted to the St. Louis Children's Hospital on May 28, the edema, cyanosis and dilated veins were again very striking. His cough was so severe as to require full doses of morphia for relief.

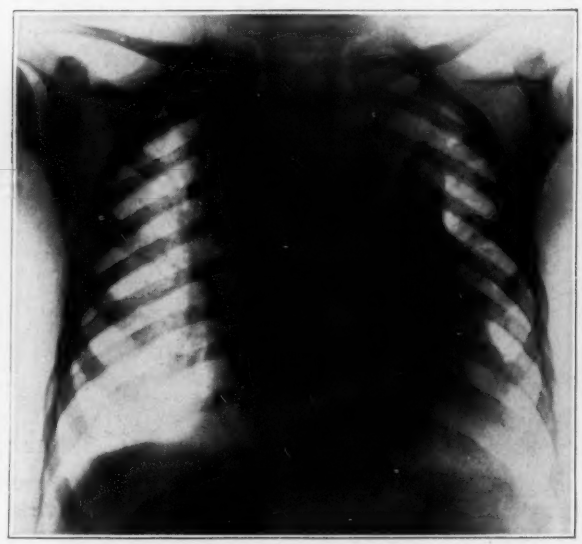

Fig. 4 (case 3).—Large mediastinal tumor in a 5 year old boy who had edema, dilated veins and cyanosis of the neck and face.

Examination.—The superficial lymph nodes and spleen were not enlarged, and the leukocytes numbered 8,400, with 84 per cent polymorphonuclears. There was no anemia, and the platelets were abundant. A roentgenogram showed a mediastinal shadow quite as extensive as in previous films, and on May 29 an irradiation of four minutes was given. There was no reaction but marked relief from the cough, and the patient slept well the following night. In two days all swelling and engorgement had completely subsided, and there were no symptoms. A second treatment of four minutes was given on June 2. Two weeks later (June 16) the edema and cough had returned, and he had a small mass the size of a lemon in the suprasternal notch. Examination of the blood showed no anemia; there were 5,200 leukocytes, with 54 per cent polymorphonuclears and no abnormal cells. By July 2, the suprasternal mass had reached the size of an orange, but there was only moderate difficulty in breathing, and he was able to play as usual. The mediastinal mass appeared unchanged on fluoroscopic examination. There was no fever, and the leukocytes were 8,600, with 72 per cent polymorphonuclears and no abnormal forms.

Course.—The clinical condition changed relatively little during the following month, except for gradual loss of energy, increase in size of the tumor in the neck and the appearance of two small tumor-like masses, one over the second left rib and the other below the xiphoid. These were firm and seemed attached to the bone. When seen on August 8, he had no superficial glandular enlargement, but the spleen could be felt and the mediastinal tumor was as before. At this time the blood showed 35,200 leukocytes, with 6 per cent polymorphonuclears, 2 per cent monocytes and 92 per cent lymphocytes. Two other examinations of the blood during the following week gave essentially the same picture. There was a moderate anemia (erythrocytes, 3,700,000), and the platelets were 81,000. Subsequently, he became weaker, the breathing was stridulous and orthopneic, and the abdomen and tumors

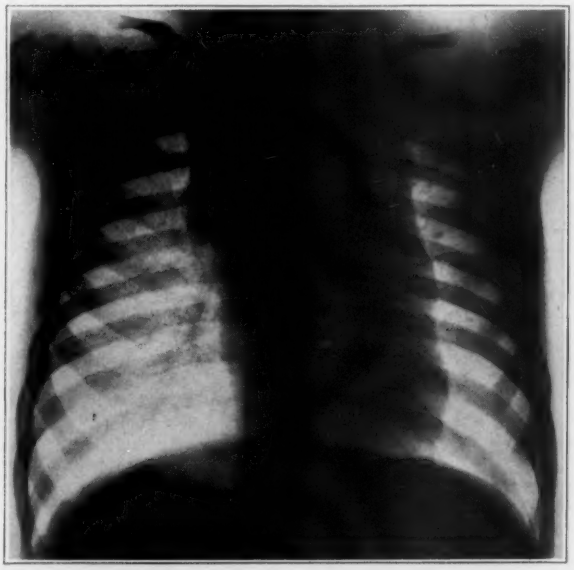

Fig. 5 (case 4).—Mediastinal tumor in a 3 year old boy, accompanied by asthmatic respiratory difficulty.

were larger. Bilateral ptosis and deafness were present during the last weeks of life but no hemorrhages. Death occurred on October 25. There was no necropsy.

CASE 4.—*History.*—S. B., a boy, aged 3½ years, began to have wheezy, asthmatic respiratory difficulty on Dec. 27, 1930. During the following month this dyspnea increased, and cyanosis was present at times.

Examination.—There were no anemia, change in the blood or glandular enlargement, and the spleen was not palpable. A roentgenogram taken on Jan. 21, 1931 (fig. 5), showed a tremendous increase in width of the mediastinal shadow from the anterior end of the fourth rib upward and extending well out into the fields of both lungs. Parasternal dulness was easily demonstrable. Irradiation was given on each of the four following days, for a total of twenty-four minutes. There was prompt relief from all respiratory difficulty after the first treatment, and at the end of a week a fluoroscopic examination showed no mediastinal shadow. Parasternal dulness was no longer present. The leukocytes on January 22 were 21,400, with 56 per cent polymorphonuclears and no abnormal cells. On February 1, they had decreased to 2,100, with 75 per cent polymorphonuclears, and ten days later there

were 21,500, with 72 per cent polymorphonuclears. By February 18, however, the leukocytes had risen to 140,000, with only 11 per cent polymorphonuclears, and the predominant cells were large nongranular lymphocytes. The platelet count was 70,000. At this time the spleen was felt 2 cm. below the costal margin, and many petechiae appeared on the skin.

Course.—During the next two months the leukocyte count varied from 2,700 to 317,000, and there was a progressive anemia in spite of several transfusions of blood. The abnormal nongranular lymphocytes continued to form a high percentage in the leukocyte count, and the platelets remained low. The cervical and submental lymph nodes became enlarged, varying in size from time to time, and the spleen increased in size. Although no further roentgen examinations were made, there was no recurrence of symptoms of respiratory obstruction. The boy died at home on April 27.

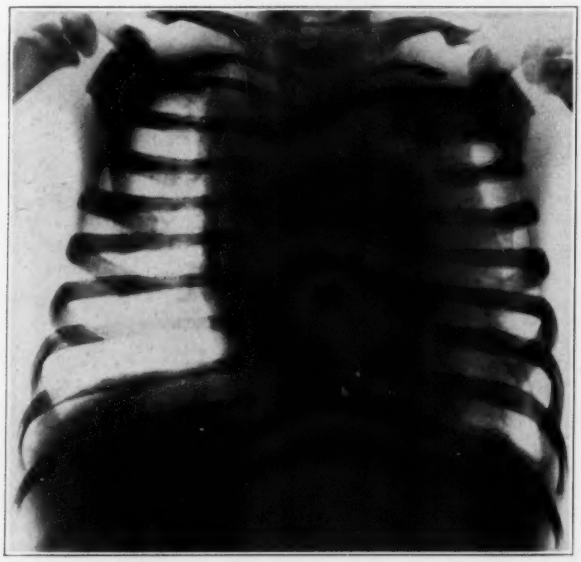

Fig. 6 (case 5).—Leukemic tumor of mediastinum in a 6 year old boy, producing severe orthopnea.

CASE 5.—*History.*—O. McN., a boy, aged 6 years, first seen on March 18, 1931, gave the history that he had had an attack of Vincent's stomatitis in March, 1930. Following measles in January, 1931, he had an attack of abdominal pain and was observed in a hospital for five days. During this time the tonsils and cervical glands were said to have become enlarged, and he began to have dyspnea and "choking spells." Since then he had lost weight, had become pale, and had complained of abnormal pain several times each day. He had been confined to bed for the past five weeks and was forced to "sleep sitting up" on account of the respiratory difficulty. During the few days preceding examination the gums bled, blood was present in the stools and red spots appeared on the skin.

Examination.—Examination showed a poorly nourished and developed boy with numerous small purpuric hemorrhages on the skin and buccal mucosa. The urine contained gross blood. The tonsils and cervical lymph nodes were much enlarged, and a firm spleen reached the umbilicus. The axillary and inguinal nodes were

small and discrete. The liver was large. Well marked parasternal dulness was present, and a roentgenogram (fig. 6) showed an enormous increase in the size of the mediastinal shadow, which extended to within 1 cm. of the left lateral thoracic wall and to the midclavicular line on the right. The leukocytes were 320,000, with 92 per cent lymphocytes, and the platelets were greatly decreased. On March 23, he was given a total of four minutes of roentgen therapy over two areas. The dyspnea increased, and he died eight hours later.

Necropsy.—Necropsy was performed (Dr. E. W. Thurston) fourteen hours post mortem.

The anatomic diagnosis was: acute leukemia with leukemic tumor in the region of the thymus gland; leukemic infiltration of the liver, spleen, kidneys and lymphatic structures, and hemorrhages into the mucous and serous surfaces, kidneys and skin.

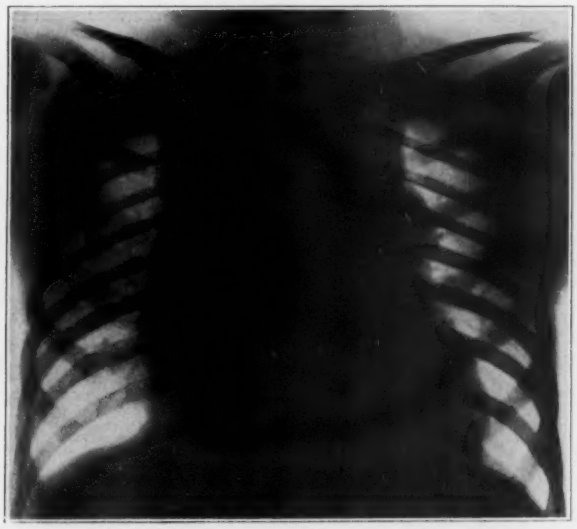

Fig. 7 (case 6).—Mediastinal tumor in a 7 year old boy with "aleukemic leukemia." There were paroxysmal cough and mild stridor.

The superior mediastinum was occupied by a large mass weighing 400 Gm. This extended over the pericardium below and pressed on the trachea above, producing a flattening of the tube. On section, the tissue was gray, cellular and arranged in lobules. Microscopically, this consisted of mononuclear leukemic cells held together by connective tissue stroma. No thymus elements were identified. Extensive infiltration of the same cells was found in the liver, kidneys and spleen and to a less extent in the other tissues. All lymphoid structures, including those of the intestinal tract, were moderately enlarged and infiltrated with the leukemic cells.

CASE 6.—*History.*—J. S., a boy, aged 7 years, an Italian, was first examined on Oct. 14, 1926. About seven weeks previously the cervical glands had become enlarged, and there was some fever. Since then there had been remissions of the fever at times, but the neck had remained considerably swollen.

Examination.—On examination, well marked bilateral cervical glandular enlargement was found, the largest nodes being the size of oranges. The axillary and inguinal nodes were slightly enlarged, and the spleen was firm and reached the umbilicus. The respirations were moderately increased, and attacks of coughing occurred at intervals after which inspiratory and expiratory stridor were present. Percussion showed marked retrosternal dulness, and a roentgenogram (fig. 7) revealed an enormous increase in the width of the mediastinal shadow, which extended to the right midscapular line on the first rib and thence down to the diaphragm. It was almost as extensive on the left side and was nodular in the level of the third rib. Biopsy of an axillary lymph node showed an abundant infiltration of mononuclear cells resembling lymphocytes, with loss of normal gland architecture, and, based on the section, a diagnosis of lymphosarcoma was made. The blood had 12,000 leukocytes, with only 5 per cent polymorphonuclears and the remainder nongranular lymphocytes. The platelets numbered 190,000 and

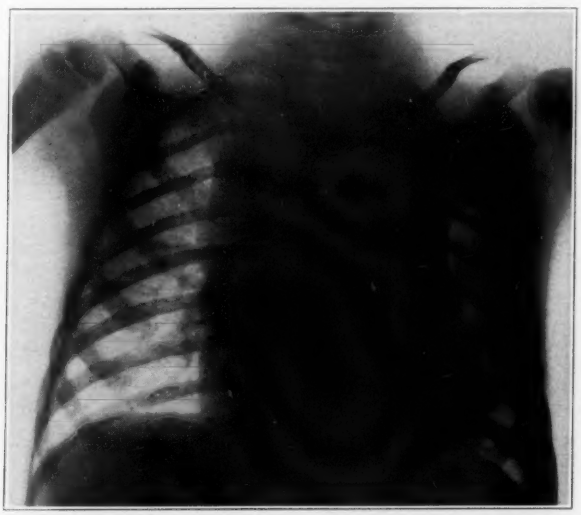

Fig. 8 (case 7).—Mediastinal leukemic tumor producing only slight symptoms of pressure in a 3 year old boy.

the erythrocytes 4,180,000. Irradiation was given on October 18, 19, 20 and 25 for a total of eight minutes. After the first three treatments there was much improvement in the cough, the stridor disappeared, and the cervical nodes decreased considerably in size. Fluoroscopic examination of the chest, however, showed little change in the mediastinal shadow. On October 27 the leukocytes had decreased to 1,900, with 92 per cent nongranular lymphocytes, and the platelets were less than 50,000. The temperature had fluctuated from 37.4 to 39.4 C. (99.3 to 102.9 F.).

Course.—The boy was removed from the hospital under protest, and died two weeks later. Because of the absence of leukocytosis, the possibility that he had lymphosarcoma was considered. The enlarged spleen and the marked decrease in polymorphonuclear leukocytes and platelets, however, with the relatively high lymphocyte count, would seem sufficient evidence to justify the diagnosis of acute leukemia in the "aleukemic" phase.

CASE 7.—*History.*—E. S., a boy, aged 3 years, had been somewhat slow in development; he walked unsteadily, and was thought to have had a cerebellar hemorrhage at birth. One week before admission on Nov. 23, 1927, he began to choke when he cried, and turned blue. He was irritable and when angry became cyanotic.

Examination.—On examination, in addition to the cyanosis on crying, there was an occasional inspiratory crow. The tonsils and the cervical lymph nodes were slightly enlarged, and a hard spleen reached 3 cm. below the costal margin. There was dulness to the right of the sternum in the first and second intercostal spaces, and a roentgenogram (fig. 8) showed great enlargement of the mediastinal shadow with somewhat irregular scalloped borders. A few subcutaneous hemorrhages were present on the extremities, and the temperature was 37.6 C. (99.7 F.). The blood showed 125,000 leukocytes, of which 92 per cent were lymphocytes. The platelets were 36,000, and the erythrocytes 3,250,000.

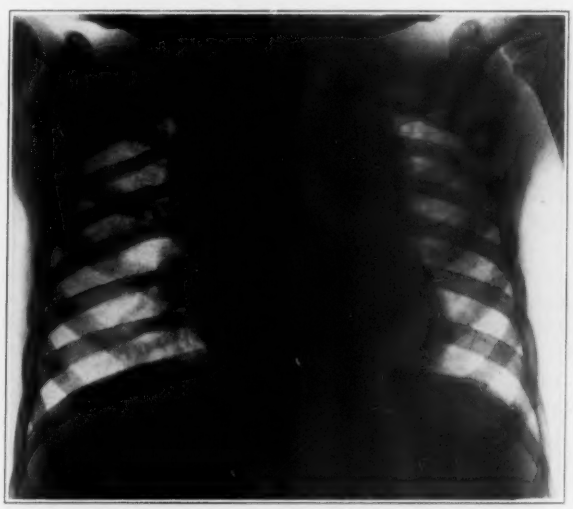

Fig. 9 (case 8).—Mediastinal mass in a 7 year old boy with leukemia but without symptoms referable to the tumor.

Course.—After the diagnosis of acute leukemia was made the patient was taken home; he died on Jan. 16, 1928. No necropsy was done.

CASE 8.—*History.*—E. P., a boy, aged 7 years, was first seen on Oct. 19, 1926, with the history of moderate asthenia for two or three months and swollen cervical glands first noted two weeks previously. Within the preceding few days the abdomen had become swollen, petechial hemorrhages appeared on the skin, and the nose bled twice.

Examination.—On examination, in addition to the hemorrhages, the liver reached the umbilicus and the spleen was 5 cm. below it. The tonsils were large, and there was a slight general glandular swelling. No respiratory difficulty was present, but a roentgenogram of the chest (fig. 9) showed a great increase in the mediastinal shadow in the supracardiac area, with irregular margins, and extending well out into the fields of both lungs. There were 400,000 leukocytes, with 98 per cent lymphocytes and very few platelets, and the erythrocytes numbered 2,550,000.

Course.—A transfusion of 230 cc. of blood was given on October 21, and on October 24, following a copious intestinal hemorrhage, the patient became stuporous and died. No necropsy was allowed.

CASE 9.—*History.*—D. K., a boy, aged 10 years, for several months had seemed to tire easily. In January, 1930, some enlarged cervical glands developed and he seemed too weak to attend school.

Examination.—He was first seen on Feb. 10, 1930; he had a temperature of 39 C. (102.2 F.) and numerous hemorrhages in the skin and oral mucous membranes. There was moderate enlargement of the cervical, axillary and inguinal lymph nodes, and the spleen reached 12 cm. below the costal margin. The blood had 200,000 leukocytes, with 99 per cent lymphocytes, and the erythrocytes were 700,000.

Course.—During the following month he continued to have cutaneous ecchymoses, bleeding from the nose and fever. There were symptoms very suggestive of acute appendicitis, but no operation was considered on account of his condition. The leukocytes varied from 18,500 to 210,000, with a very low percentage of polymorphonuclears and more than 90 per cent of nongranular lymphocytes. At no time were any symptoms of respiratory obstruction noted. Although several transfusions of blood were given, the anemia continued, and the temperature ranged between 38 and 40 C. (100.4 and 104 F.). Death occurred on March 11.

Necropsy.—Necropsy was performed five hours post mortem (Dr. M. G. Smith). The anatomic diagnosis was: acute lymphatic leukemia with extensive leukemic infiltration of the liver, spleen, kidneys and bone marrow; enlargement of the lymph nodes, thymus and intestinal lymphoid tissue; hemorrhages into the skin, mucous and serous surfaces, kidneys and lungs; extensive lobular pneumonia, and perforation of infiltrated appendix, walled off by adhesions.

The thymus, greatly enlarged and lobular, measured 14 by 8 by 3 cm. and extended down over the pericardium. On section, it was cellular and microscopically densely infiltrated with rather large mononuclear cells so that no normal thymic structure was identified. The infiltrating cells extended into the surrounding fat so that the margin of the gland was not distinguishable. They were apparently identical with those infiltrating the liver, spleen, kidneys, lymphoid structures and marrow. The lymph nodes at the pulmonary hilus as well as those of the mesentery were moderately enlarged. The appearance of the appendix led to the suspicion that its rupture was related to the swelling and friability of the wall, resulting from the extensive leukemic infiltration.

COMMENT

Certain features in connection with this group of cases of leukemia with mediastinal tumor and those noted by other authors (table) deserve comment.

Sex.—All of the nine children whose cases are reported here were boys. A similar striking sex selectivity is apparent in the tabulation of seventy-one other instances from the literature in which the sex was noted (table). Of these only twelve were girls. This combined ratio of sixty-eight males to twelve females, or 5⅔:1, is sufficiently large to indicate that sex is a very important factor in the occurrence of leukemic mediastinal tumors. Acute leukemia alone shows a rather constant tendency for males to predominate over females in the pro-

portion of 2:1. This ratio was found in three hundred and ninety-eight cases collected by Ward; in fifty-seven by Minot and Isaacs; in one hundred and thirteen by Warren and in eighteen by Vogel. In forty-six cases of acute leukemia in children under 15 years of age, observed in the St. Louis Children's Hospital, there were thirty boys and sixteen girls. A comparison of the sex incidence of chloroma, another type of tumor accompanied by acute leukemia, may be made by quoting the figures given by Dock and Warthin, who collected thirty-eight cases of which twenty-nine were males and nine were females, a ratio of about 3:1.

Age.—Seven of the nine children were under 8 years of age. A tabulation of these with seventy-four other reported cases (table) shows that thirty-one occurred in the first decade; twenty-three in the second, twenty-one in the third, four in the fourth and four in the fifth. The fact that seventy-five of the eighty-three patients, or over 90 per cent, were under 30 and that two-thirds were under 20 illustrates a special susceptibility in the early decades of life. Acute leukemia presents a similar, although somewhat less marked, predilection for these younger ages. Ward, for example, in the total number of his cases found about 70 per cent under 30 years old, with 55 per cent under 20, and Minot and Isaacs reported approximately the same age incidence in fifty-seven cases.

Size and Location of the Tumor.—The size of the mediastinal tumors, as shown by the roentgenograms, is impressive, and they can well be termed massive. A comparison of them will show a certain similarity in all the cases illustrated. In one child (case 5) the mass in the thymic region weighed 400 Gm., and in the instances of other reported cases (table) in which the dimensions are given, the volume of tissue involved is considerable. The location is constantly in the superior and anterior mediastinum, and, from the organs of the neck above, the tumor spreads down over the pericardium and often laterally in two wings. Its nodular arrangement as seen at necropsy is shown in the roentgenograms by rounded irregularities of the borders. In all instances the mass occupies the position in which the thymus is found in infancy and is of approximately the same shape, although this may be due to its moulding by the surrounding structures. The character of all the tumors examined at necropsy is similar. They consist of a fairly firm, gray, translucent, cellular tissue with a tendency to be arranged in lobules, adherent to the sternum and pericardium and at times to the structures at the base of the heart. The surrounding tissues are not grossly invaded in the manner of malignant neoplastic growths, although portions of the pleura are sometimes thickened by a similar infiltration. The lymph nodes in the vicinity are often enlarged, but not always, and are usually distinct from the main tumor, although

sometimes embedded in it. Microscopically, the cells composing the mass are mononuclear and indistinguishable from those present in the blood, which infiltrate the bone marrow, lymph nodes, spleen, liver and kidneys in such cases and also in cases of acute leukemia not accompanied by thoracic tumors. Mitotic figures are usually easily found, although this is also true of other leukemic infiltrations. At the edges of the mass the cells have a tendency to infiltrate the surrounding connective tissues, but not, as previously mentioned, by growth of considerable masses of cells into adjacent structures. It is rare that any remnants of thymic structure, such as either the small thymic cells or Hassall's corpuscles, can be recognized, and it has been urged by Margolis that in leukemia the thymic cells undergo an involution and hypoplasia.

The question of whether such leukemic mediastinal masses have their origin in the thymus gland is of some interest since thymic elements are absent. Mediastinal lymph nodes would seem to form the only other source of origin in this location, but the lobular character of the mass, its "thymus-like" appearance, and its total lack of resemblance to enlarged nodes would seem to exclude this possibility. The previously mentioned tendency to occur in younger persons would also favor the assumption of a thymic origin because of the fact that thymic tissue tends to disappear in later life. It is probable, therefore, that such mediastinal enlargements originate in the thymus or its remnants even though characteristic thymic structures are not demonstrable.

The clinical symptoms of the mediastinal involvement are apparently entirely the result of mechanical pressure, and consist of cough, dyspnea and cyanosis of varying degree. They tend to be paroxysmal and are often precipitated or accentuated by muscular effort. In certain cases the intrathoracic pressure of the mass has produced edema of the face and neck with cyanosis, and the respiratory embarrassment has been orthopneic. One of the children under our observation was thought at the outset to be suffering from bronchial asthma because of the attacks of dyspnea. The proportion of patients showing clinical symptoms of pressure is hard to determine from the reported cases, but it would seem that more than half have shown well defined evidence of respiratory embarrassment. There were many, however, with large thoracic masses in whom no such symptoms have been noted. In a certain number of instances the mediastinal mass has been accompanied by a considerable accumulation of sterile bloody fluid in the left pleural cavity, and in two cases it has been noted that the right pupil has been larger than the left. The accompanying clinical manifestations of leukemia have shown the usual variations noted in this disease.

The fact that the mediastinal tumor has been present before the leukemic changes in the blood appeared in certain cases, as, for example, in four of those here reported, is of much interest. This has been

thought by some observers to mean that the mediastinal growth was primary and in some way incited the production of the leukemia, as Sternberg assumed in his hypothesis of the neoplastic nature of "leukosarcoma." Such, however, is not the only possible explanation. If one believes, as the evidence indicates, that in acute leukemia the essential dysfunction, and consequently the origin of the abnormal cells present in the blood, is in the bone marrow, it is possible to conceive that such local tumor masses as those found in the mediastinum and elsewhere result from secondary infiltrations of cells originating in the marrow and carried there by the blood. It is not unusual to observe instances of acute leukemia in which the blood shows no leukocytosis (aleukemic leukemia), but at necropsy there is a tremendous infiltration of the spleen, lymph nodes and such parenchymatous organs as the liver and kidneys by leukemic cells. This would indicate a tendency for certain of the body tissues to remove from the blood abnormal circulating leukocytes. With such a mechanism it might be assumed that when the leukemic changes in the marrow are in an early stage and the abnormal cells begin to reach the circulation, they are removed, and consequently do not accumulate in the blood stream. It may be that only later, when the abnormal cells appear in large numbers, is the blood picture of acute leukemia recognized. Such a conception would explain better the findings in the first child (case 1), who, in addition to the mediastinal tumor (fig. 3), had much enlarged cervical lymph nodes (fig. 1 *A*) several weeks before the blood showed leukemic changes. Even at this early period section of a slightly enlarged axillary lymph node showed the presence of a dense infiltration of abnormal mononuclear cells. Similar "preleukemic" infiltration of lymph nodes distinct from the mediastinal mass has been noted by Landau. While it is not generally believed that the leukemic cells multiply in the circulating blood, the presence of mitotic figures in both the localized and more diffuse tissue infiltrations of acute leukemia suggests that local multiplication of these cells occurs in the tissues. The hypothesis of a neoplastic or "sarcomatous" origin of such localized masses as occur during, or immediately preceding, an acute leukemia is widely quoted, but it would seem that this is still quite as speculative as the theory that all acute leukemia is neoplastic in origin. The nature of acute leukemia is at present unknown, but of the proposed hypotheses, that of a neoplastic origin has few advocates among hematopathologists.

The abruptness with which the blood picture may change from normal to leukemic is illustrated in the case reported by Borchardt. In this patient a blood count of 14,000, with 93 per cent polymorphonuclears, had changed in two days to 91,800, with 94 per cent lymphocytes. In one of the children whose case is here reported (case 4) the leukocytes were 21,500, with 72 per cent polymorphonuclears, and a

week later 140,000, with 11 per cent polymorphonuclears and the remainder nongranular lymphocytes, but in none of the other patients were the counts made at sufficiently short intervals to detect a sudden alteration in the blood picture.

The effect of the roentgen rays on the leukemic mediastinal masses has been striking when used before the blood picture of leukemia was present. Four of the children whose cases are reported here were treated by irradiation in the "preleukemic" period, and all showed remarkable clinical improvement. The symptoms of respiratory embarrassment were much less marked after twenty-four hours and were gone a day or so later. The mediastinal shadow had completely disappeared within a week in three of the patients, but the fourth showed little change and had a recurrence of pressure symptoms. The irradiation was usually followed by a fall in the leukocyte count, with no significant change in the differential ratio. In two children (cases 1 and 2) with enlarged cervical lymph nodes the irradiation produced a rapid disappearance of these (fig. 1 *A* and *B*), as well as of the mediastinal mass. Since the lymph nodes were not in the area directly irradiated, it seems likely that at least a part of the effect of the roentgen rays on these "preleukemic" tumors is due to the irradiation of the blood. In six other cases collected from the literature and abstracted earlier in this paper, irradiation was employed before the blood was leukemic. Five of these showed a prompt disappearance of the thoracic tumor, but in two the mass returned. In the single instance (no. 51) in which roentgen therapy apparently precipitated the acute leukemic manifestations, the patient received an unusually large amount of irradiation (five hours), and it seems likely that this may have influenced the result. In the others, the interval after irradiation before blood changes appeared was four months in three, three months in two, six weeks in three and two weeks in one. After the leukemic picture had appeared, death followed in from a few weeks to two months.

When the blood picture of acute leukemia had developed in the patient with mediastinal tumor before irradiation, this treatment was of no benefit, and there is some evidence that it accelerated the final outcome. One patient of this type under our observation (case 5) died somewhat unexpectedly eight hours after the first treatment, while another (case 6) lived for three weeks. In the reports of three other cases in which irradiation with the roentgen rays was given, Zohman's patient lived four days and those of Gorlitzer and Borchardt died in three and four weeks, respectively. None was improved. In only two cases has irradiation with radium been mentioned, and in each instance the child died within a few hours, the first (no. 52) living six hours, and the other (no. 48) dying suddenly on the following day. These reports are in accord with other observations of the harmful effect of

irradiation on patients with acute leukemia (Minot and Isaacs, and Wood), and seem to contraindicate this form of therapy when the blood picture of acute leukemia is present.

The duration of the disease is somewhat difficult to estimate, since the mediastinal enlargement may be present for some time before it reaches sufficient size to produce symptoms. In the table, the duration of each case is shown as nearly as it could be estimated. From the appearance of the earliest symptoms of respiratory distress the patients lived from one to seven months, usually less than four. The ones who had no pressure signs and were observed only with the symptoms of acute leukemia usually lived only from one to two months. This has also been the common duration of life of other patients after the blood picture of acute leukemia has developed.

The differential diagnosis of masses in the anterior mediastinum in children commonly includes, in addition to the leukemic tumors, the possibility of lymphosarcoma and Hodgkin's disease. Because of the different location of enlargements limited to the lymph nodes at the pulmonary hilus, as well as of primary tumors of the lung or pleura, it would seem unlikely to mistake them for mediastinal masses. I have observed at the St. Louis Children's Hospital only four children with lymphosarcoma involving the mediastinum, and on one of these my observation was not continued long enough to exclude the possibility of the later development of acute leukemia, while no case of mediastinal Hodgkin's disease has occurred. The nine instances of mediastinal tumor associated with acute leukemia observed would indicate that this is the most frequent type of mediastinal enlargement occurring in children.

Probably the most interesting feature of leukemic mediastinal tumors lies in speculation about their origin, whether they are true neoplastic tumors or "leukosarcomas" with unrestrained local cellular proliferation and secondary metastatic manifestations, or whether they consist essentially of extensive local infiltrations and accumulations of abnormal cells originating elsewhere and deposited in the mediastinum from the blood stream because of some chemotactic influence. Those who favor the neoplasm hypothesis can cite the observation of the instances in which the tumor has reached a considerable size before the abnormal cells appear in the blood; the presence of numerous cellular mitoses in the tumor, as in sarcomas; the tendency of the cells to spread beyond the original capsule of connective tissue and into the surrounding fat, and the similarity of these characteristics to those of sarcomatous growths. On the other hand, those who do not believe in the neoplastic origin of acute leukemia feel that the foregoing features may be explained on another basis; that one of the characteristics of the disease is the presence of infiltrations of the leukemic cells in such parenchyma-

tous organs as the liver and kidneys in addition to the spleen and lymphatic tissues, and that the local tumor masses in the mediastinum and elsewhere are manifestations of a similar infiltration. A study of the clinical and pathologic characteristics of this series of cases has left the impression that the latter hypothesis is the more plausible.

SUMMARY

The cases of nine boys with massive leukemic enlargements of the thymic region are reported. In four the clinical symptoms of pressure preceded the blood picture of acute leukemia, and in these cases irradiation with the roentgen rays produced marked relief from the respiratory distress. In three the mediastinal tumor disappeared completely and permanently within a few days, although all died later of acute leukemia.

It seems likely that such mediastinal involvement is more frequent in acute leukemia than is generally recognized, since the nine instances reported occurred in a series of thirty-eight cases.

A review of the cases of eighty-three patients, including those here reported, shows that the condition affects males almost six times as frequently as females, and that over 90 per cent have occurred in persons under 30 years of age.

Although irradiation has usually produced a temporary beneficial effect on the mediastinal tumor if employed before blood changes were present, such irradiation by roentgen rays or radium afterward seems not only to be without benefit, but in certain instances to have hastened the time of death.

The study of the clinical and pathologic reports of the observed cases has given the impression that the mediastinal mass is the result of infiltration by leukemic cells carried there by the blood stream rather than a true neoplastic tumor arising in situ. Whatever its nature, the condition is sufficiently characteristic, as determined by modern methods of clinical examination, to be readily recognized and to merit consideration as a clinical entity in acute leukemia. The data presented indicate that its occurrence is more common than is usually appreciated.

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THE BIOLOGIC RELATIONSHIP BETWEEN COW'S, GOAT'S AND HUMAN CASEINS

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Clinical observations indicate the possibility that there is an immunologic relationship between human, cow's and goat's milks. It is a matter of common experience that eczema and other manifestations of hypersensitiveness in the nursing baby are frequently aggravated by the addition of cow's milk, and conversely that eczema in the milk-sensitized infant is unrelieved by reverting to human milk or by the substitution of goat's milk. The work of Fleischer [1] Bauer,[2] Wells [3] and von Versell [4] suggested that this interrelationship may reside in a biologic similarity of the caseins of the three milks. The establishment of this fact seemed to be of sufficient importance, because of its practical application, to warrant further investigation. With this end in view, we undertook a series of experiments in which we used purified cow's, human and goat's caseins. The results of this work form the basis of the present communication.

The caseins that were used in the experiments were prepared by the following method.

From the Department of Pediatrics, Cornell University Medical College and the New York Nursery and Child's Hospital, New York City; and from the Department of Pediatrics, Harvard Medical School and The Children's Hospital, Boston.

1. Fleischer, G. W.: Russk. Vrach **7** (pt. 2) :1638, 1908; abstr., Centralbl. f. Path. **20**:308, 1909.

2. Bauer, J.: Ueber den Artcharakter der Milcheiweisskörper, Klin. Wchnschr. **47**:830, 1910.

3. Wells, H. G.: Studies of the Chemistry of Anaphylaxis: III. Experiments with Isolated Proteins, Especially Those of the Hen's Egg, J. Infect. Dis. **20**:147, 1911.

4. von Versell, Arnold: Ueber das serologische Verhalten von Milch und Milcheiweisskorpern in frischem und gekochtem Zustand, Ztschr. f. Immunitätsforsch. u. exper. Therap. **24**:267, 1915-1916.

METHOD OF PREPARATION

Cow's Casein.—Fat-free raw milk was used entirely. Early in the work, the casein was precipitated with tenth-normal acetic acid, following the determination of the maximum precipitation point by repeated titrations of the milk. Later, it was prepared by the method of Van Slyke and Baker.[5] This permits of the removal of the insoluble calcium caseinate and calcium phosphate at a point just below the iso-electric point, thereby rendering the casein much more soluble.[6] One per cent solutions of this product were obtained by dissolving 0.1 Gm. of casein in 9 cc. of physiologic solution of sodium chloride and 1 cc. of tenth-normal solution of sodium hydroxide.

Human Casein.—The raw milk was centrifugated to remove the fat. It was then dialyzed against distilled water to remove the buffer salts. Early in the work, it was precipitated with twentieth-normal acetic acid. Later, it was found that by using a partially buffered solution of twentieth-normal lactic acid and fortieth-normal sodium hydroxide in the apparatus described by Van Slyke and Baker for the preparation of cow's casein [5] a much larger yield of a readily soluble casein could be obtained.[6] Two per cent solutions of the product were obtained by dissolving 0.2 Gm. of casein in 9.2 cc. of physiologic solution of sodium chloride and 0.8 cc. of tenth-normal solution of sodium hydroxide.

Goat's Casein.—The fat of raw milk was removed by centrifugation. The casein was precipitated by the addition of tenth-normal acetic acid. It was then freed from electrolytes by washing with water and was dried with alcohol and ether. One per cent solutions of the product were obtained by dissolving 0.1 Gm. of casein in 9 cc. of physiologic solution of sodium chloride and 1 cc. of tenth-normal solution of sodium hydroxide.

ACTIVE SENSITIZATION

This phase of the work consisted of the active sensitization of guinea-pigs with one of the caseins and subsequent attempts to produce anaphylaxis with one of the other caseins.

Negative controls in each experiment consisted of normal animals that were given intravenous injections of the second casein. In none of these animals were the injections attended by any evidences of shock or untoward disturbances that simulated anaphylaxis. Positive controls consisted of animals that were sensitized by the intraperitoneal route to the first casein and were subsequently given intravenous injections of the same casein. In all of these, the second injection resulted in violent anaphylaxis.

EXPERIMENTS

GROUP 1.—Forty-six animals were sensitized to cow's casein by the intraperitoneal route. From seventeen to twenty-one days later they were given human casein intravenously. The results are summarized in table 1.

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5. Van Slyke, L. L., and Baker, John C.: The Preparation of Pure Casein, J. Biol. Chem. **52**:127, 1918.

6. Casein prepared by this method was used entirely in the experiments on passive sensitization and precipitin tests and to a large extent in those on active sensitization.

Of the forty-six animals, thirty-two presented evidence of an immunologic relationship between the two caseins.

It seemed of interest to determine whether or not the animals that were anaphylactic but recovered after the injection of human casein were desensitized to the original antigen, cow's casein. Accordingly, thirteen animals in this group were given a second injection of cow's casein within a few hours. All of these animals died in typical shock. This seems to indicate that complete desensitization to the original antigen did not occur. These results are similar to those obtained by Wells [3] in his experiments on the relationship between cow's and goat's caseins, in which he found that desensitization to the original and sensitizing antigen did

TABLE 1.—*Guinea-Pigs Sensitized to Cow's Casein Intraperitoneally; from Seventeen to Twenty-One Days Later, Human Casein Was Given Intravenously*

a. Animals died in anaphylactic shock*	8
b. Animals anaphylactic but recovered	24
c. Equivocal signs	6
d. No evidence of anaphylaxis	8
Total	46

* In the preparation of the data shown in this and the following tables, the criteria of anaphylaxis in all of these animals were convulsions, severe respiratory difficulty, involuntary twitchings and frequently transitory paralyses of the extremities, sneezing, ruffling of the coat, loss of sphincter control and bucking.

TABLE 2.—*Guinea-Pigs Sensitized to Human Casein Intraperitoneally; from Seventeen to Twenty-One Days Later, Cow's Casein was Given Intravenously*

a. Animals died in anaphylactic shock	2
b. Animals anaphylactic but recovered	14
c. Equivocal signs	5
d. No evidence of anaphylaxis	16
Total	37

not occur after recovery from severe anaphylaxis that was induced by the injection of the opposing casein. The significance of this we shall discuss later.

GROUP 2 (Reverse of Group 1).—Thirty-seven animals were sensitized to human casein by the intraperitoneal route. From seventeen to twenty-one days later, they were given cow's casein intravenously. The results are summarized in table 2.

Of the thirty-seven animals, sixteen presented evidence of an interreaction between the caseins.

It is of interest to note that of the twelve animals in the group that were anaphylactic but recovered after the injection of cow's casein and were subsequently given injections of human casein ten died in a state of anaphylactic shock. These findings are analogous to those obtained in the animals in group 1 and point to a lack of complete desensitization to the original antigen.

Confirmatory evidence for the findings in groups 1 and 2 was sought by means of the Schultz-Dale phenomenon. Accordingly, six female guinea-pigs were actively sensitized to cow's casein. From seventeen to twenty-one days later, a uterine horn was removed and suspended in Ringer's solution. A solution of human casein was then added to the bath. In three of the experiments there was

a sharp response to the introduction of the human casein. On addition of the original antigen, cow's casein, however, there was a second and greater reaction on the part of the uterine strip (chart 1). Similarly, in two of six experiments on animals that were previously sensitized to human casein, there was an immediate response of the uterine strip when a solution of cow's casein was added, and a second and complete contraction when the original antigen, human casein, was subsequently introduced (chart 2). These results are in keeping with those obtained in the preceding experiments in active sensitization.

GROUP 3.—Twelve animals were sensitized to goat's casein by the intraperitoneal route. From seventeen to twenty-one days later, they were given human casein intravenously. The results are summarized in table 3.

TABLE 3.—*Guinea-Pigs Sensitized to Goat's Casein Intraperitoneally; from Seventeen to Twenty-One Days Later, Human Casein was Given Intravenously*

a. Animals died in anaphylactic shock	1
b. Animals anaphylactic but recovered	8
c. Equivocal signs	0
d. No evidence of anaphylaxis	3
Total	12

TABLE 4.—*Guinea-Pigs Sensitized to Human Casein Intraperitoneally; from Seventeen to Twenty-One Days Later, Goat's Casein Was Given Intravenously*

a. Animals died in shock	2
b. Animals anaphylactic but recovered	2
c. Equivocal signs	0
d. No evidence of anaphylaxis	0
Total	4

In nine of the twelve animals, there was evidence of an interreaction between the two caseins.

It is of interest that two animals in the group that were anaphylactic but recovered after the injection of human casein died in anaphylactic shock when subsequently given injections of the original antigen.

GROUP 4 (Reverse of Group 3).—Four animals were sensitized to human casein by the intraperitoneal route. From seventeen to twenty-one days later they were given goat's casein intravenously. The results are summarized in table 4.

In all of the animals comprising this group, there was an interrelationship between the two caseins. Both animals that were anaphylactic but recovered after the injection of goat's casein died in anaphylactic shock when subsequently given injections of the sensitizing antigen.

The findings in groups 3 and 4 are comparable to the results obtained in groups 1 and 2 and point to the same similarity between human and goat's caseins as exists between cow's and human caseins.

GROUP 5.—Eight animals were sensitized to cow's casein by the intraperitoneal route. From seventeen to twenty-one days later they were given goat's casein intravenously. The results are summarized in table 5.

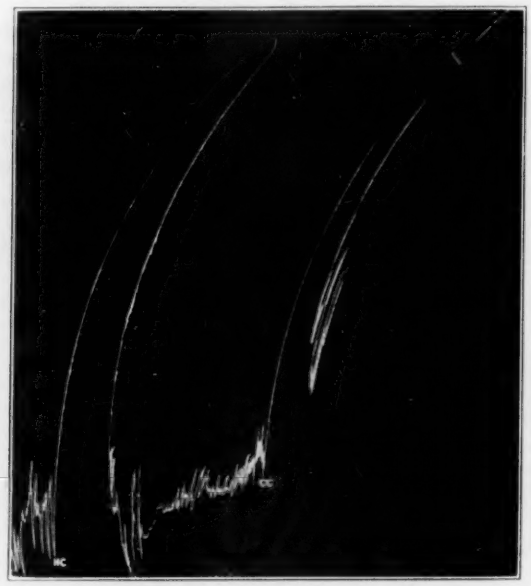

Chart 1.—Results of the Dale test, showing response of uterine muscle to cow (*CC*) and human (*HC*) caseins in guinea-pigs originally sensitized to cow's casein.

Chart 2.—Results of the Dale test, showing response of uterine muscle to cow (*CC*) and human (*HC*) caseins in guinea-pigs sensitized to human casein.

In five of the eight animals there was an interreaction between the two caseins.

GROUP 6 (Reverse of Group 5).—Three animals were sensitized to goat's casein. Seventeen days later they were given cow's casein intravenously. The results are summarized in table 6.

In all of the animals in this group there was an interreaction between the two caseins.

The results of experiments in groups 5 and 6 are in keeping with those reported for the four preceding groups, and indicate a relationship between cow's and goat's caseins comparable to that found to exist between cow's and human, and human and goat's caseins.

TABLE 5.—*Guinea-Pigs Sensitized to Cow's Casein Intraperitoneally; from Seventeen to Twenty-One Days Later, Goat's Casein Was Given Intravenously*

a. Animals died in anaphylactic shock	3
b. Animals anaphylactic but recovered	2
c. Equivocal signs	0
d. No evidence of anaphylaxis	3
Total	8

TABLE 6.—*Guinea-Pigs Sensitized to Goat's Casein Intraperitoneally; from Seventeen to Twenty-One Days Later, Cow's Casein Was Given Intravenously*

a. Animals died in anaphylactic shock	0
b. Animals anaphylactic but recovered	3
c. Equivocal signs	0
d. No evidence of anaphylaxis	0
Total	3

PRECIPITIN TESTS

In this phase of the work, we endeavored to determine the ability of known anti-cow's casein and anti-human casein rabbit serums to precipitate the opposite antigen.

Anti-cow's casein serum was obtained by actively immunizing rabbits by the intravenous injection of 5 cc. of a 1 per cent solution of cow's casein every second day for a period of two weeks. Only serums with titers for cow's casein of at least 1:500 were used in the tests. It was found early in the work that both cow's casein and human casein were only weakly precipitinogenic and that their anti-serums rarely gave a precipitin titer of greater than 1:200. Later we were able to increase the titer to 1:500 by using rabbits that previously had been immunized to another and entirely unrelated protein, such as eggwhite, as recommended by Parker[7] for the preparation of pollen extract precipitins. Anti-human casein serum was obtained in a similar manner, with 5 cc. of a 2 per cent

7. Parker, J. T.: Production of Precipitins for Ragweed Pollen, J.Immunol. **9**:515 (Nov.) 1924.

solution of human casein as the antigen. Serums yielding a titer of at least 1:500 were used throughout.

The tests for precipitin were made as follows: A 1 per cent solution of cow's casein and a 2 per cent solution of human casein were diluted to 1:20, 1:50, 1:100, 1:250, 1:500 and 1:1,000. To each of these dilutions were added 0.1 and 0.2 cc. of the opposite immune serum. The tests were read after one hour's incubation at 37.5 C., and again after the solution had stood on ice for eighteen hours. Controls of normal rabbit's and human serum were used throughout. Dilutions of the casein solution without the addition of serum and immune serum diluted with physiologic solution of sodium chloride also served as controls. Only tests that showed distinct flocculation were recorded as positive. They may be summarized as follows: 1. Anti-cow's casein rabbit serum, which gave a precipitin titer to cow's casein of 1:500, regularly precipitated human casein in a dilution of 1:300. 2. Anti-human casein rabbit serum, which gave a precipitin titer to human casein of 1:500, precipitated cow's casein in a dilution of 1:250.

In brief, the immune serums contained precipitins that reacted to both caseins, although the titer was considerably weaker for the opposite antigen. These findings are comparable to those obtained in the experiments in active sensitization.

TABLE 7.—*Guinea-Pigs Passively Sensitized to Cow's Casein by the Intraperitoneal Injection of Anti-Cow's Casein Rabbit Serum; Twenty Hours Later, Human Casein Was Given Intravenously*

a. Animals died in anaphylactic shock	0
b. Animals anaphylactic but recovered	15
c. Equivocal signs	9
d. No evidence of anaphylaxis	3
Total	27

PASSIVE SENSITIZATION

In these experiments we passively sensitized guinea-pigs with known anti-cow's casein and anti-human casein rabbit serums and attempted subsequently to produce anaphylaxis with the opposite antigen.

GROUP A.—Twenty-seven guinea-pigs were passively sensitized by the intraperitoneal injection of from 1 to 3 cc. of anti-cow's casein serum, prepared by the method described in the report of the precipitin tests. From eighteen to twenty-one hours later, the animals were given 1 cc. of a 2 per cent solution of human casein intravenously. The results are summarized in table 7.

Of the twenty-seven animals, fifteen showed evidence of an interreaction between the caseins. Of these, six were within four hours given injections of the original antigen, cow's casein. Five of these six animals died in a typical state of shock.

Positive controls consisted of a group of six guinea-pigs that were passively sensitized to cow's casein in the same manner as the test animals and later given the original antigen, cow's casein, intravenously. All of these controls died in a state of anaphylactic shock. Negative controls consisted of a second group of five normal guinea-pigs, not previously sensitized with immune serum, which were given human casein intravenously. The results in these animals were uniformly negative.

GROUP B.—Twenty guinea-pigs were passively sensitized by the intraperitoneal injection of from 1 to 3 cc. of anti-human casein serum obtained by the method previously described. From eighteen to twenty-one hours later, they were given 1 cc. of a 1 per cent solution of cow's casein intravenously. The results are summarized in table 8.

Of the twenty animals, nine presented evidence of an interreaction between the two caseins. Eight of the animals with positive reactions were subsequently given a second injection of human casein, and, of these, seven died in typical shock.

Four animals, passively sensitized in the same manner as the test animals, and subsequently given human casein intravenously died in a state of anaphylactic shock. Of four normal guinea-pigs that did not receive immune serum but that were given cow's casein intravenously, none presented any untoward signs. These two groups served as positive and negative controls, respectively.

The results of these experiments in passive sensitization are strikingly similar to those obtained in the work on active sensitization. In both there is strong presumptive evidence of an interreaction between cow's and human caseins. Also, complete desensitization did not occur following the induction of anaphylaxis.

TABLE 8.—*Guinea-Pigs Passively Sensitized to Human Casein by the Intraperitoneal Injection of Anti-Human Casein Rabbit Serum; Twenty Hours Later, Cow's Casein Was Given Intravenously*

a. Animals died in anaphylactic shock	0
b. Animals anaphylactic but recovered	9
c. Equivocal signs	8
d. No signs of anaphylaxis	3
Total	20

COMMENT

These experiments indicate a close immunologic relationship between the caseins of cow's, goat's and human milks. It would appear, therefore, as previously suggested by Versell,[4] that casein occupies a position analogous to lens and testicular proteins, in that it is not species-specific but possesses characteristics that are common to a number of different species.

The results that we obtained seem to point to slight chemical differences in the three caseins. Evidence of this is the failure of one casein completely to desensitize the animal against the sensitizing casein. This could be explained by the assumption that human, cow's and goat's casein each contain two distinct antigenic fractions. One of these is species-specific and sensitizes only to itself. The other antigenic factor is common to the three species. This assumption would explain at the same time the antigenic relationship of the different varieties of casein and also their specificity. A possible analogy to these variations is found in the experiments of Dochez and Avery,[8] Zinsser and Parker[9]

8. Dochez, A. R., and Avery, O. T.: The Elaboration of Specific Soluble Substance by Pneumococcus During Growth, J. Exper. Med. **26**:477, 1917.

9. Zinsser, H., and Parker, J. R.: Further Studies on Bacterial Hypersusceptibility: II., J. Exper. Med. **37**:275, 1923.

and Heidelberger and Avery [10] on the type-specific substance in the body fluids of patients with pneumonia, in which it was shown that antigenic substances derived from such closely allied organisms as the various types of pneumococci possess certain distinct chemical and biologic characteristics that clearly differentiate the types.

It seems to us that these findings may be of practical as well as of academic importance. Clinical experience has shown that a certain number of "milk hypersensitive" infants are markedly benefited when a change from cow's milk to human or goat's milk is made. In some of these infants, skin tests have revealed hypersensitiveness to lactalbumin of cow's milk, and it is reasonable to suppose that many more would react similarly if they were studied carefully. In view of the biologic dissimilarity between the whey proteins of the various milks, it is readily understood why such substitution measures are successful in this group of children. Unfortunately, however, this procedure is either only partially successful or entirely unsuccessful in a large number of infants who manifest allergic symptoms when fed cow's milk. It is possible that these failures may be due to sensitization to cow's milk casein rather than to lactalbumin. In this event, the substitution of human milk or of goat's milk for cow's milk would merely constitute a replacement by another biologically similar problem.

SUMMARY

1. Experiments in active sensitization revealed that cow's, human and goat's caseins sensitize against each other.

2. Anti-cow's casein serums gave positive precipitin reactions to human casein, and anti-human casein serums reacted positively with solutions of cow's casein.

3. Animals that were passively sensitized to cow's casein exhibited evidences of anaphylaxis when given human casein intravenously. The converse was equally true.

4. The results that were obtained seem to indicate a close biologic relationship between cow's, human and goat's caseins. It is possible that this similarity may explain certain difficulties that are encountered in the treatment of allergic states by the substitution of one milk for another.

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10. Heidelberger, M., and Avery, O. T.: The Soluble Specific Substances of Pneumococcus, J. Exper. Med. **38**:73, 1923. Avery, O. T., and Heidelberger, M.: Immunologic Relationships of Cell Constituents of Pneumococcus, ibid. **38**:81, 1923.

RELATION OF MEASLES AND TUBERCULOSIS IN YOUNG CHILDREN

A CLINICAL AND ROENTGENOGRAPHIC STUDY

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Opinions vary as to the effect of measles on young children infected with active or presumably quiescent tuberculosis. Until recent years measles was always considered to be a menace to a tuberculous child, and was thought frequently to reactivate an apparently quiescent tuberculous process. At present there are several observers, such as Groer [1] and Choffé,[2] who believe that measles is not as harmful as it was previously supposed.

Nobécourt, Liège and Herr [3] recently reported a clinical, roentgenologic and pathologic study of twenty children with tuberculosis that subsequently were infected with measles. Roentgenograms of the chest were made after the termination of the measles. They stated, "Tuberculosis has no effect on measles, but measles, in many cases, has an effect on tuberculosis." As little or nothing is known of the changes that occur in the chest of children with tuberculosis during and immediately after measles, it was our purpose to determine these changes as far as possible by roentgenologic methods. It was hoped that these roentgenograms would perhaps help us in studying the changes in the chest, the character of these changes and, finally, their progress.

METHOD AND MATERIAL

This study is based on the examination of twenty children who were admitted to the Willard Parker Hospital because of measles.

The children were from 10 months to 7 years of age, thirteen being under 3 years, seven under 5 years and one under 7 years (see table).

From the Willard Parker Hospital for Contagious Diseases, Department of Hospitals.

1. Groer, F., in Engel, S., and Pirquet, C.: Handbuch der Kindertuberkulose, Leipzig, Georg Thieme, 1930, vol. 2, p. 948.

2. Influence of Measles and Whooping Cough on Tuberculosis in Children, Foreign Letter, J. A. M. A. **94**:1157 (April 12) 1930.

3. Nobécourt, P.; Liège, R., and Herr, A.: Rougeole et tuberculose, Arch. de méd. d. enf. **33**:65 (Feb.) 1930.

There were eight white children, nine Negroes and three children of Porto Rican parentage.

We feel reasonably certain that all these patients had been infected with tuberculosis before measles. A positive intracutaneous tuberculin test was obtained, from eight to twenty days after the measles, in all but two of the children while at the Willard Parker Hospital. In the two cases in which no test was done, necropsy revealed an old tuberculosis. These children died eight and eighteen days, respectively, after the onset of measles. In twelve of the cases there was a record of a positive tuberculin reaction obtained in another institution some time before the measles. In only four cases was the tuberculosis first suspected at the Willard Parker Hospital, and these cases all showed pulmonary involvement. Since thirteen of these children were under 3 years of age, the original tuberculous infection could not have been of long standing. One cannot be certain, of course, as to the activity of the tuberculosis just before the measles.

As confirmatory evidence of tuberculosis, necropsies were performed in five cases (nos. 1, 2, 3, 17 and 19). All these cases showed tuberculous lesions in the lungs or elsewhere. From the histories and necropsy findings one can be certain that the tuberculosis had been present before the measles. One other patient died, but no necropsy was performed. This case had been closely observed before, during and after the measles. The clinical course and roentgenographic findings, such as cavity formation, widening of the superior mediastinum and a probable pericarditis, made us feel certain that the child had tuberculosis.

In four other cases there was bacteriologic or histologic evidence of tuberculosis. In case 6, tuberculous cervical lymph nodes had been removed before the measles; the patient in case 11 had been operated on for tuberculous dactylitis; in case 13 tubercle bacilli had been found in the urine, and in case 12 tuberculous osteomyelitis of the spine developed soon after the measles.

In six additional cases (nos. 8, 9, 10, 14, 15 and 20) there was a history of intimate contact with a parent or relative who had an active pulmonary tuberculosis.

The four remaining cases showed: In case 7 a large serous effusion had been present for at least a month before the measles. This effusion had been considered tuberculous. The effusion had not been entirely absorbed fourteen months after the measles. In case 16, the history, clinical course and roentgenographic findings were those seen in tuberculosis. In case 18, the clinical course after the measles was mild; the roentgenographic findings, however, were those usually seen in tuberculosis. Finally, in case 5, there was extensive pulmonary infiltration in the region of the interlobar fissure between the right upper and middle lobes. After eleven months a sharply outlined triangular

shadow remained in this region. This type of infiltration was first described by Sluka,[4] and is seen almost exclusively in tuberculosis.

In most of the cases the tubercle bacillus was searched for in smears from pharyngeal swabs, sputum or feces. In no case was the tubercle bacillus found in these examinations before, during or after measles. The contents of the stomach were not examined.

The roentgen methods in the Willard Parker Hospital were similar to those used in previous studies.[5] Successive roentgenograms of the chest were taken every few days during the children's stay in the hospital. A physical examination was made whenever a roentgenogram was taken. The cases were then followed in an institution or at home after the patients' discharge from the Willard Parker Hospital. If any of the children had been in an institution before the onset of the measles, a full history and the original roentgenograms were obtained. In all, a hundred and seventy-two roentgenograms were studied: thirty-seven before, thirty-nine during and ninety-six after measles. We were able to obtain roentgenograms of fifteen of the twenty children before their measles. Two children died at the Willard Parker Hospital. We followed all of the remaining eighteen for periods varying from two to twenty months.

The roentgen technic employed at the Willard Parker Hospital was as follows: The exposures were made at a distance of 91.5 cm. (36 inches), using a 15 cm. (6 inch) point spark gap with a voltage of 55 kv. and 100 ma. of current. The time of exposure was one tenth of a second. Except in a few instances, the roentgenograms were taken in the sitting position in both the postero-anterior and direct lateral positions.

The right and left lateral positions were used because there is a clearer visualization of the lymphatics of the posterior mediastinum and also those localized at the bifurcation of the trachea. Often the denseness, size and position of the shadow cast by these lymphatics make one suspect tuberculosis. The lateral exposures also enable one to ascertain a pleural involvement in the region of the interlobar fissures between the various lobes. The shadow cast by the interlobar involvement may appear either as a fine line or as a large opacity. The latter finding indicates a wide separation of the fissures. One may also see occasionally, using the lateral position, a retrosternal opacity along the anterior wall of the chest, close to the base, which probably represents a pleural effusion.

4. Sluka, E.: Die Hilus Tuberkulose der Kinder im Roentgenbild, Wien. klin. Wchnschr. **25**:259 (Feb. 15) 1912.

5. (*a*) Kohn, J. L., and Koiransky, H.: Successive Roentgenograms of the Chest of Children During Measles, Am. J. Dis. Child. **38**:258 (Aug.) 1929; (*b*) Roentgenographic Reexamination of the Chests of Children from Six to Ten Months After Measles, Am. J. Dis. Child. **41**:500 (March) 1931.

Because of the tendency of young children to move, we devised an immobilizing apparatus [6] for taking roentgenograms of the chest. The details of this apparatus have been published elsewhere.

DESCRIPTIVE DATA

The cases studied were too few for a statistical study of any value. There was a variation, however, in the clinical course and in the roentgenographic changes in the pulmonary system of the patients during and after measles. These variations can best be illustrated by the histories and perhaps will give some information as to the effect of measles on the tuberculosis in these young children.

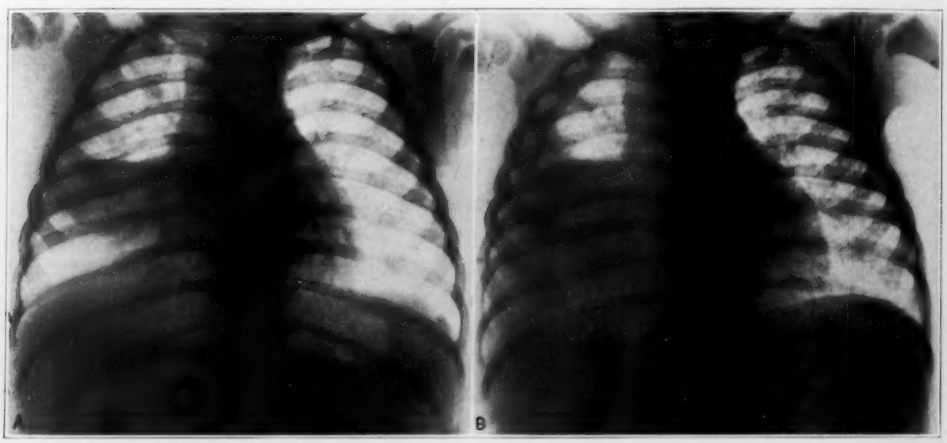

Fig. 1.—*A,* appearance of the lungs in case 3 (R. J., aged 13 months) on June 19, 1930, during the recession of the measles rash. The temperature was high, there being some impaired resonance in the right axilla and base of the right lung, but no bronchial breathing was heard. The roentgenogram shows a dense opacity in the middle section of the right lung field. There is also an opacity at the level of the first rib anteriorly. There is an increase in the size and density of the hilar shadow, with a widening of the right superior mediastinum. A fine line indicative of pleural thickening is seen along the costal border of the right lung. *B,* appearance on Aug. 15, 1930, two months later. A large dense band reaches from the apex to base in the right axillary region. There is a large opacity occupying the lower two thirds of the right lung field. The diaphragm is not visualized. This shadow had gradually increased in size. Throughout the remainder of the right and left lung there is a scattered mottling, which is probably due to numerous areas of infiltration. There is a widening of the right superior mediastinum. Post mortem the right lower lobe was found to be a caseating mass. The rest of both lungs was studded with miliary tubercles. There was also a thickened pleura over the right lung and caseating hilar and paratracheal lymph nodes.

6. Kohn, J. L., and Koiransky, H.: Immobilizing Apparatus for Taking Chest Roentgenograms in Young Children, Am. J. Roentgenol. **25**:100 (Jan.) 1931.

I. There were cases in which, previous to or at the onset of the measles, there had been a small area of pulmonary infiltration plus involvement of the mediastinal lymph nodes. The clinical and roentgenographic evidence of the pulmonary infiltration made one suspect that it was tuberculosis. During the measles the infiltration became larger and continued to progress until a large portion of the lung had become involved and death ensued (fig. 1). Apparently no attempt at repair had set in. The pleura or pericardium also became involved in some instances. A further increase in the widening of the superior mediastinum and an increase in density and size of the hilar shadow were also seen. Clinically, the measles was usually mild, but the condition soon after became progressively worse. Physical signs over the lungs corresponded to the roentgenographic findings. Fever was present continuously after the onset of the measles. There were four cases that could be put in this group (nos. 1, 2, 3 and 4).

CASE 3.—R. J., a colored boy, aged 13 months, was admitted to the Nursery and Child's Hospital on May 16, 1930. There was no history available. While at this hospital the patient had symptoms of an infection of the upper respiratory tract, but continued to have a low grade fever after the respiratory symptoms had subsided. The Wassermann reaction of the blood was negative and the intracutaneous tuberculin test with amounts up to 2 mg. remained negative.

The patient was admitted to the Willard Parker Hospital on June 8 for measles, with an early rash and enlargement of the cervical nodes; the chest was clear. However, a roentgenogram of the chest taken during the recession of the rash showed a dense opacity in the middle section of the right lung and enlarged hilar shadows, with a widening of the right superior mediastinum. An intracutaneous tuberculin test was positive on June 28. The child's condition gradually became worse, and there were signs of fluid and consolidation at the base of the right lung. The temperature rose to 103 F. every day, and successive roentgenograms of the chest showed a progressive enlargement of the opacity until the entire base of the right lung was involved. There was also a localized effusion of the pleura.

On August 14, the child was transferred to the Sea View Hospital, and on Aug. 23 there were signs of tuberculous meningitis. He died on September 1. The sputum was negative for tubercle bacilli.

Necropsy showed a small amount of serous fluid in the pericardium. The hilar lymph nodes were transformed into large caseous masses. Both lungs had many scattered miliary nodules with a slight tendency to grouping and fusing in mulberry-shaped masses. The lower lobe of the right lung was almost entirely transformed into a caseous mass which was fairly firm. Both lungs were entirely wrapped in thickened pleura, and very small air space was left in them. There were scattered tubercles in the liver, spleen and kidneys, and a jelly-like exudate at the base of the brain.

CASE 4.—A. J., a colored girl, aged 2½ years, was admitted to Bellevue Hospital on Nov. 10, 1930, with a history of eight months of poor health, fever and loss of weight. There was no history of contact. Examination showed acute phlyctenular conjunctivitis of the right eye. Large cervical nodes were present and the lungs were normal except for dulness and diminished breathing at the angle of the right scapula. An intracutaneous tuberculin test was positive.

While at Bellevue Hospital the child had fever nearly all the time, and numerous roentgenograms of the chest showed enlarged hilar nodes with a circumscribed infiltration occupying the lower one third of the right lung field adjacent to the cardiac border.

The child was admitted to the Willard Parker Hospital for measles on Feb. 9, 1931, with Koplik spots and an early rash. Examination of the chest revealed fine râles and dulness in the right axilla and the base of the right lung but no bronchial breathing. Roentgenograms of the chest showed the opacity in the right lower lobe to be much larger than previously, and also an increase in size and density of the hilar nodes. The left lung was normal. The child was never very sick. The first few days the temperature was about 102 F. and later about 100 F. A tuberculin test performed just before the patient's discharge was positive.

The child was transferred back to Bellevue Hospital on February 20, and did poorly. She continued to have fever and lost weight. The dulness and râles at the base of the right lung persisted, and the patient finally died, on June 1. Roentgenograms seemed to show a breaking down and cavity formation in the area of pulmonary infiltration. There was a tremendous enlargement of the hilar shadow and also the heart shadow, which made one suspect a tuberculous pericarditis. There was no meningitis. No necropsy was performed.

II. There were cases in which, previous to the measles, there had been perhaps a small area of pulmonary infiltration plus involvement of the mediastinal lymph nodes. During the measles, instead of enlargement of this infiltration, scattered pulmonary opacities were seen in one or both lungs (figs. 2, 3 and 5 *A*). These pulmonary opacities were similar to those often seen in a diffuse tuberculous bronchopneumonia. There was also a further increase in the size and density of the hilar shadow. A lateral view often showed dense lymphatic enlargement in the posterior mediastinum and also at the bifurcation of the trachea. Shadows at the site of the interlobar fissures were also seen (figs. 3 and 4). During the measles the children were usually very sick, had a high fever and were very dyspneic. There were dulness and fine râles, with scattered areas of bronchial breathing over one or both lungs. These physical signs usually persisted for several weeks and then, as the patients improved, gradually receded.

Knowing that the children had been infected with tuberculosis before the measles, one was at first tempted to interpret all the infiltrations as tuberculous. However, most of the infiltrations cleared up in a comparatively short time. One or two years later calcified hilar nodes and some exaggeration of the pulmonary markings in scattered areas were seen (fig. 5 *B*). There were four cases that could be placed in this group (nos. 10, 12, 13 and 16).

CASE 13.—J. P., a white girl, aged 1½ years, was admitted to Bellevue Hospital on Aug. 26, 1928, because of an abscess on the right shoulder. Following an incision this healed, but a few days later an infection of the upper respiratory tract developed, and urinalysis showed casts and red blood cells. The fever gradually receded, but on November 10 there was a recurrence of the respiratory infec-

tion. A tuberculin test at this time was positive. The child's father had died of pneumonia but the mother was alive and well. The infection of the respiratory tract grew worse, râles being heard all over the chest with bronchial breathing over the right upper lobe. The child had fever which lasted about three months. After this, there was an occasional rise in temperature with slight dulness and râles over the right upper lobe. During her entire stay at the Bellevue Hospital the patient had some pus in her urine. Cystoscopy showed a plug in the right ureter. Tubercle bacilli were found in the urine.

Numerous roentgenograms showed signs of infiltration in the lower portion of the right upper lobe and the upper portion of the right middle lobe. This infiltration was adjacent to the heart. There was also a widening of the upper mediastinum.

The patient was transferred to the Metropolitan Hospital on April 5, 1929, and a roentgenogram at that time showed large ill defined shadows in the region of the right hilus.

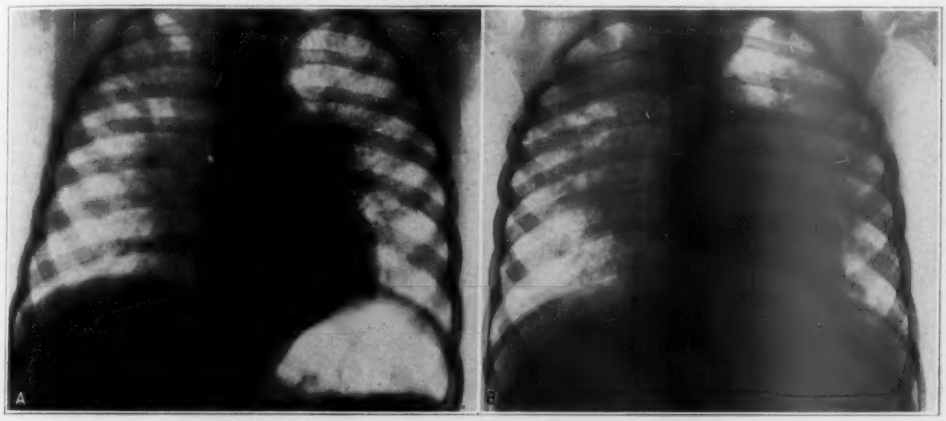

Fig. 2.—*A*, appearance of the lungs in case 13 (J. P., aged 3½ years) on Feb. 28, 1930, the second day after the appearance of a measles rash. The temperature was high. There were scattered areas of bronchial breathing at the base of both lungs posteriorly. The roentgenogram shows greatly enlarged and dense hilar shadows with a large number of ill defined opacities throughout both lung fields but confluent mainly in the region of the right upper lobe and in the middle section of the left lung contiguous with the hilar shadows. Roentgenograms taken ten months before showed large ill defined shadows in the right hilar region. *B*, appearance on March 7, one week later. The rash is gone; the high fever persists and the bronchial breathing is still present. The roentgenogram shows further enlargement of the hilar shadows with an increase of infiltration in the upper portion of the right lung and the middle section of the left lung. Within the hilar areas, dense elliptic opacities, probably lymph nodes, are seen.

The child was admitted to the Willard Parker Hospital because of chickenpox on Jan. 19, 1930. She was returned to the Metropolitan Hospital, but on February 26, she was readmitted to Willard Parker Hospital for measles. On admission there were Koplik spots and a very early rash. The patient was very sick and had dyspnea, dulness over both lungs, with fine râles and scattered areas

of bronchial breathing at the bases of both lungs. For two weeks the patient's condition was poor and the bronchial breathing persisted. After one week more, the bronchial breathing in the right lung had cleared, but there was still bronchial breathing near the left scapular angle. The child was transferred back to the Metropolitan Hospital on April 5.

During her entire stay at the Willard Parker Hospital the child had a temperature between 102 and 104 F. A roentgenogram of the chest taken during measles showed a large number of ill defined opacities throughout both lung fields, confluent mainly in the region of the right upper lobe, and the middle section of the right lung contiguous to the hilar shadow with widening of the hilus. Lateral examination showed involvement of the interlobar fissures, with

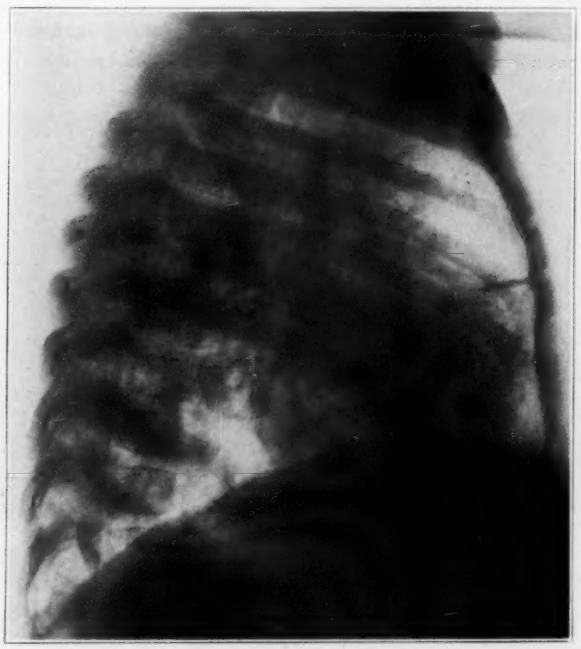

Fig. 3.—Lateral view taken March 13 (six days after *2B*) in case 13. The high fever persists and the bronchial breathing is diminished. There is a coarse irregular line of increased density running across the lung field toward the sternum at the site of the interlobar fissure between the right middle and right lower lobes. There are also large dense conglomerate opacities above, below and behind the bifurcation of the trachea, presumably lymph nodes. Scattered infiltrations are seen in the lung fields.

large dense masses seen below, behind and above the bifurcation of the trachea. Subsequent roentgenograms at the Willard Parker Hospital showed only a slight decrease in the extent of the pulmonary infiltrations.

On the patient's readmission to the Metropolitan Hospital, on April 5, the fever persisted for over two months. The bronchial breathing gradually cleared up, but the fine râles at the bases of both lungs persisted. After June 15 the child had an occasional rise in temperature. On November 29, her general con-

dition was good and resonance over the lungs was normal, but coarse râles were heard throughout. Soon after this an infection of the upper respiratoy tract developed with an otitis media which, on December 24, necessitated a double mastoid operation. On April 11th, 1931, the mastoid wound was still draining and a few coarse râles were heard over the chest. During June, 1931, a severe phlyctenular conjunctivitis of the right eye developed. This healed slowly, with scar formation at the upper part of the corneoscleral junction. There was no temperature reaction at this time. On November 30, the child was in good condition and the mastoid was still draining, but the lungs were clear.

Roentgenograms taken while the patient was at the Metropolitan Hospital showed a gradual clearing of the pulmonary infiltration. At present there are only increased pulmonary markings in the upper half of the right lung, with a moderate enlargement of the right hilar region, within which several calcified areas are seen.

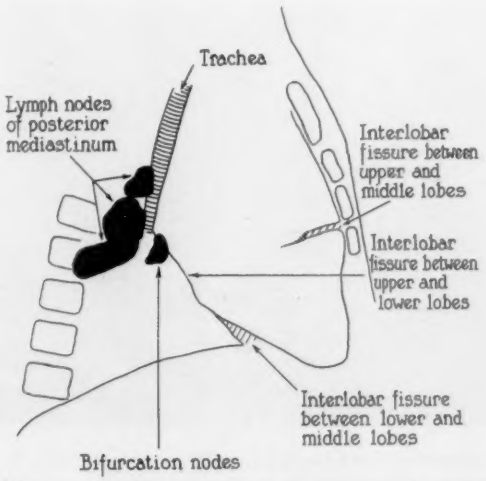
Trachea
Lymph nodes of posterior mediastinum
Interlobar fissure between upper and middle lobes
Interlobar fissure between upper and lower lobes
Interlobar fissure between lower and middle lobes
Bifurcation nodes

Fig. 4.—A diagrammatic sketch of the roentgenogram shown in figure 3, depicting enlarged, dense, tuberculous lymph nodes with involvement of interlobar fissures.

Case 10.—J. M., a white boy, aged 3 years, was admitted to the Lincoln Hospital on Jan. 20, 1930, because of enlargement of the cervical nodes of three weeks' duration. The child's mother had active tuberculosis. On physical examination the chest was normal. The tuberculin test was positive and the roentgenogram of the chest showed a definite enlargement of both hilar regions, with an area of pulmonary infiltration on the left side at the level of the second intercostal space.

The child was transferred to the Willard Parker Hospital on February 13 because of measles. There were Koplik spots and an extensive rash. The child was very sick, and fine râles were heard at the bases of both lungs. He continued to be sick for about two weeks and all this time he had a high fever; the fever persisted until February 28. On the patient's discharge, râles were still heard over the right lung. The left lung was clear. The tuberculin test was positive. Many roentgenographic examinations showed small defined opacities throughout the right lung, confluent in the region of the right middle lobe and

also in the left intercostal region. There were enlarged hilar shadows, and a lateral examination showed an interlobar involvement between the right upper and right lower lobes and also between the right upper and middle lobes.

The child was transferred back to the Lincoln Hospital on March 3, where he remained until May 20. While at the Lincoln Hospital he had a left purulent otitis media and an acute tonsillitis with cervical adenitis. Roentgen examination showed a persistence of the infiltration in the left lung.

The child was transferred to the Sea View Hospital on May 20, and after admission his lungs were clear, he gained weight and there was no fever. Various roentgenograms taken since then showed the hilar shadow to be gradually growing smaller. A shadow in the left lung was interpreted as a fibrotic infiltration in the second intercostal space. The child was last seen in August, 1931, and was doing very well. The roentgenogram of the chest was about the same.

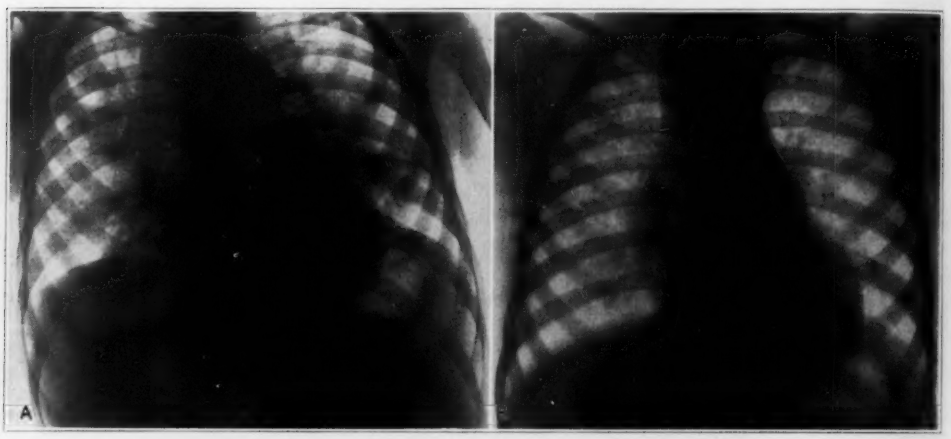

Fig. 5.—*A*, appearance on March 27 (two weeks after fig. 3) in case 13. The temperature is lower. The lungs are clearing, but there is still some bronchial breathing at the base of the left lung. There is a slight increase in the extent of the infiltration. The hilar shadow is the same. *B*, appearance on December 15, ten months later. The child's condition is improved, the fever is gone and there are a few coarse râles at the base of both lungs. The roentgenogram shows a moderate enlargement of the right hilar region, within which are several calcified nodes. There is an exaggeration of the pulmonary markings in the upper half of the right lung.

III. There was one case in which, previous to the measles, there had been, perhaps, a small area of pulmonary infiltration. Soon after the measles a large homogeneous shadow was seen in the right upper lobe. This shadow persisted for a long time, with little temperature reaction and few abnormal physical signs. The child did well after discharge. Similar cases have been described by Soto and Ontiveros[7]

7. Soto, L. Y., and Ontiveros, J.: Infiltraciones pulmonares paraespecifices en los niños, Arch. españ. de pediat. **13**:658 (Nov.) 1929.

and Nobécourt [3] following measles in children previously infected with tuberculosis.

In this group could also be included a case showing a large dense hilar shadow and a large triangular opacity in the region of the interlobar fissure between the right upper and middle lobes (fig. 6 *A*). As previously mentioned,[4] this type of infiltration is found almost exclusively in tuberculosis.

CASE 8.—J. M., a white boy, aged 7 months, was admitted to Bellevue Hospital on April 20, 1930. The mother had pulmonary tuberculosis, and on examination the child was poorly nourished, with signs of rickets and enlarged right cervical lymph nodes. He occasionally had a temperature of 101 F., and his weight remained stationary. The tuberculin test was positive. A roentgenogram

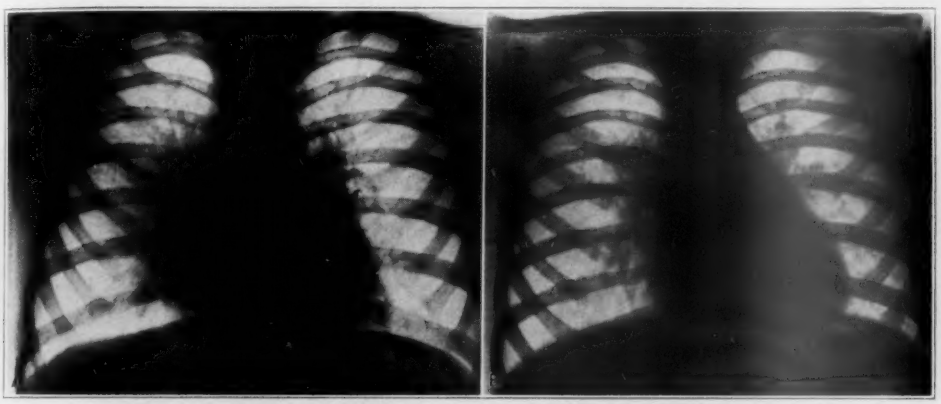

Fig. 6.—*A*, appearance of the lungs in case 5 (I. McG., aged 3 years) on March 5, 1930, during the height of the measles rash. The temperature was about 104 F. Fine râles were heard all over the chest. The roentgenogram shows both hilar regions to be enlarged and increased in density, with coarse strands radiating into the lung field, especially at the right. At the interlobar fissure between the right upper and middle lobes there is a large irregular wedge-shaped opacity with its base toward the hilar shadow and its apex pointing toward the axilla. Numerous calcified shadows, probably lymph nodes, are seen in the hilar shadow. *B*, appearance on Nov. 14, 1930, eight months later. The lungs are clear and the child is in excellent condition. The roentgenogram shows the wedge-shaped opacity to be still present but denser and more sharply defined at the site of the interlobar fissure.

showed a distinct widening of both the right and left upper mediastinum, which was sharply outlined.

The child was transferred to the Metropolitan Hospital on June 20, where he had an uneventful stay.

He was transferred to the Willard Parker Hospital with measles on July 17. On examination there were Koplik spots and an extensive rash. The lungs were clear, the child not being very sick. He had fever only on the day of admission. The tuberculin test was positive the day before discharge. Roentgenograms of the chest showed the right paravertebral region to be obscured

by a dense opacity gradually shading off toward the middle section of the right lung. There was an enlargement of both hilar regions, and a lateral examination showed enlargement of the lymphatics in front, below and behind the bifurcation of the trachea.

The child was readmitted to the Metropolitan Hospital on July 24, and on examination there was some dulness in the right suprascapular region, the breath sounds being normal. The child, however, had fever for over a month after admission and lost over 2 pounds (9 Kg.) in two months. When she was last examined, on May 11, 1931, her chest was clear and she was gaining slowly. Roentgenograms taken at various times showed a persistence of the opacity in the region of the right upper lobe. However, on March 14, the lungs were clear, roentgenographically, but there were still an increase in the hilar shadows and a widening of the upper mediastinum.

CASE 5.—I. McG., a white girl, aged 3 years, was admitted to the Metropolitan Hospital as a foundling; no history was obtained. On admission she had vaginitis. No roentgenogram was taken.

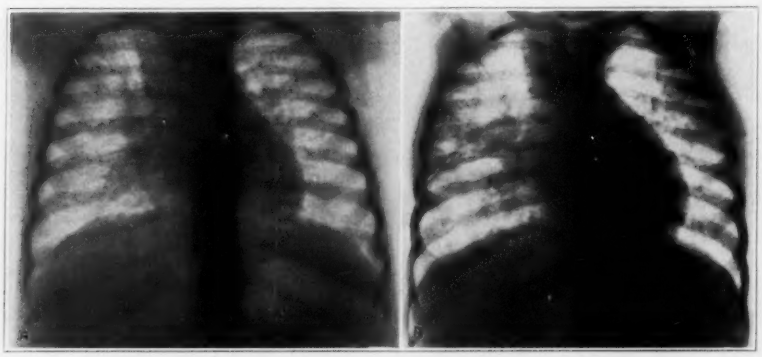

Fig. 7.—*A*, appearance of the lungs in case 20 (C. C., 15 months old). This child was having expiratory difficulty, and wheezing was heard most of the time. The roentgenogram, taken on April 22, 1931, shows an infiltration in the lower two thirds of the right lung field adjacent to the hilar shadows. There is an increase in the size and density of the right hilar shadow, with a widening of the superior mediastinum, especially on the right (paratracheal adenopathy). There are two fine lines at the site of the interlobar fissure between the right upper and right middle lobes. *B*, appearance three weeks later (May 12), during the height of the measles rash. The fever was high and there was bronchial breathing at the base of the right lung. The pleural shadow between the right upper lobe and the right middle lobe is increased. There is a large area of infiltration, honeycombed in appearance, just above the interlobar fissure. At the outer part of the infiltration there is a pea-shaped shadow with a lighter center, possibly the site of the original tuberculous infection. The shadows of the hilus, the superior mediastinum and the infiltration at the base of the right lung are denser than previously.

The child was transferred to the Willard Parker Hospital on March 2, 1930, because of measles, with Koplik spots and a very early rash. After a few days, fine and coarse râles were heard all over the chest, and the temperature returned to normal after four days. The tuberculin test was positive on March 10. Roent-

genograms taken during the height of measles showed a large irregular wedge-shaped opacity, with its base towards the hilar shadow in the region of the interlobar fissure between the right upper and middle lobes (fig. 6 *A*). The hilar shadow was large with denser shadows within, which were probably lymph nodes. Five days later the roentgenogram showed a retrogression of the consolidation, the wedge-shaped opacity being smaller.

The child was sent back to the Metropolitan Hospital on March 12; the lungs gradually cleared, but there was a return of fever for about two weeks, and then occasional fever occurred every few weeks. The child was discharged on February 6, in good condition; she was gaining weight and the lungs were clear. Roentgenographic examination before discharge still showed the wedge-shaped opacity, but it was denser and more sharply defined (fig. 6 *B*).

IV. There were two cases that illustrated the effect of measles on the so-called primary pulmonary complex. During the measles there was an additional hazy area of infiltration surrounding the site of pul-

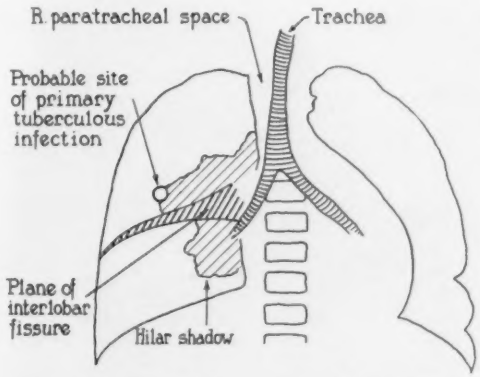

Fig. 8.—Diagrammatic sketch of the roentgenogram shown in figure 7, depicting the site of the primary tuberculous infection, with the enlarged right hilus overlapping the primary focus, and involvement of the interlobar fissure.

monary infiltration from which strands radiated toward the hilar region (figs. 7 *B* and 8). This hazy area entirely disappeared within a few days.

Case 19.—T. W., a white boy, aged 14 months, was admitted to the New York Foundling Hospital on Jan. 2, 1931, for swelling of the second finger of the right hand and dorsum of the left hand. No previous history was obtained. The child's lungs were clear, he had fever only occasionally and the tuberculin test was positive. Roentgenograms showed involvement of the third, fourth and fifth left metacarpal bones, and of the second phalanx. A roentgenogram of the chest showed enlargement of the paratracheal and bronchial lymph nodes, more clearly defined on the right. A small area of infiltration in the periphery of the right lung in the region of the fifth rib was seen (primary focus). The tuberculin test was positive.

The child was admitted to the Willard Parker Hospital for measles on March 8, 1931, with fading Koplik spots and a diffuse rash. Examination showed scars on both buttocks, a purulent discharge from both ears and swelling of the posterior

cervical glands. The dactylitis was the same as already mentioned. The chest was clear. The patient had fever for five days after admission and a secondary rise four days later. Roentgenograms of the chest showed enlargement of the paratracheal and right hilar glands, with a small irregular infiltration in the right lung at the level of the sixth rib posteriorly. A few hazy strands of increased density were seen connecting this area of primary pulmonary infection with the right hilar shadow.

The child was transferred back to the Foundling Hospital and then to the Metropolitan Hospital. His chest was clear, but phlyctenular conjunctivitis of the left eye developed. There was fever for four days after the patient's discharge from the

Fig. 9.—Right lateral view in case 20 on May 12, showing large dense conglomerate shadows in front, below and behind the bifurcation of the trachea. A fine line is seen running across the lung from the vertebra to the sternum at the site of the interlobar fissure of the right upper and middle lobes. Another line is seen running downward and forward from the posterior mediastinum to the diaphragm at the site of the interlobar fissure between the right lower and right middle lobes. There is also an opacity at the base of the lung close to the retrosternal region, as described previously and shown in the diagram.

Willard Parker Hospital. He was doing well until April 25, when there was evidence of meningitis. He died on April 28. A roentgenogram of the chest before he died showed no changes.

Necropsy showed no free fluid in the pleura. The right lung showed small caseating nodules in the parenchyma of the right lower lobe. The left lung showed

several small reddish nodules in the parenchyma of the middle of the left lobe, but these were not caseating. The peribronchial nodes were small, there being moderate caseation on the right side. The mesenteric nodes were not involved. A gelatinous exudate and tubercles were found at the base of the brain.

CASE 20.—C. C., a colored girl, aged 11 months, was admitted to the Harlem Hospital on March 11, 1930, because of fever and cough of eight weeks' duration. Since birth the child had been exposed to the tuberculosis of a relative who subsequently died of that disease. On admission the patient's general condition was good, and chest percussion gave normal results; sibilant and sonorous râles were heard throughout the chest. The tuberculin test was positive. Soon after admission a peculiar hacking cough developed, with attacks of dyspnea, perhaps owing to large tuberculous glands compressing the large bronchi. The temperature varied from 101 to 105 F. and the respirations were rapid. Roentgenograms showed large hilar shadows and an increase in the size of the superior mediastinum.

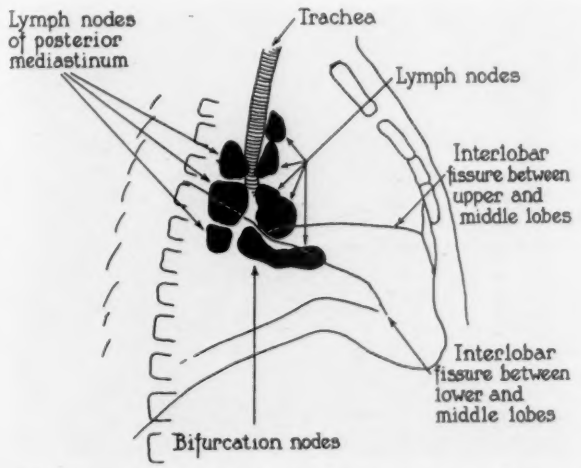
Lymph nodes of posterior mediastinum
Trachea
Lymph nodes
Interlobar fissure between upper and middle lobes
Interlobar fissure between lower and middle lobes
Bifurcation nodes

Fig. 10.—Diagrammatic sketch of the roentgenogram shown in figure 9, depicting interlobar fissures and large, dense, comglomerate tuberculous lymph nodes.

with evidence of infiltration in the major portion of the base of the right lung. There were also some small areas of infiltration in the left upper lobe.

The patient was transferred to the Sea View Hospital on Jan. 2, 1931, in poor condition and coughing. The cervical nodes were enlarged, and the chest was the same as before. Examination of the feces, pharyngeal smears and urine for tubercle bacilli yielded negative results. At Sea View Hospital the patient's temperature was usually about 100 F., there being an occasional rise to 103 F. She gained 1 pound (0.4 Kg.) in weight, but the expiratory dyspnea and wheezing were present most of the time. There was constant dulness in the right intrascapular region. Numerous roentgenograms taken at this hospital continued to show an infiltration in the lower two thirds of the lung field adjacent to the hilar shadow, while the shadow itself remained the same as previously. There were two fine lines at the site of the interlobar fissure between the right upper and right middle lobes (fig. 7 *A*).

The child was transferred to the Willard Parker Hospital on May 9, because of measles, with Koplik spots and a profuse rash. She was not very sick; sibilant râles were heard throughout the chest, with bronchial breathing at the base of the right lung. There was fever on the day of admission only. Roentgenograms taken during the measles showed a large area of infiltration, honeycombed in appearance, just above the interlobar fissure. At the outer part of the infiltration there was a pea-shaped shadow, with a lighter center, possibly the site of the original tuberculous infiltration. The interlobar shadow between the right upper and middle lobes was increased over that seen at the previous examination, and the shadows of the hilar region and the superior mediastinum, as well as the infiltration at the base of the right lung, were larger than before the measles (figs. 7 *B* and 8). A lateral roentgenogram showed dense shadows below, behind and in front of the bifurcation of the trachea. There was also evidence of pleural involvement at the site of the interlobar fissure, between the right upper and middle

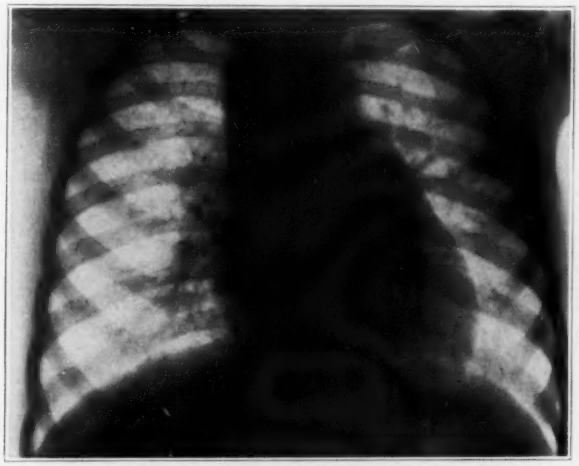

Fig. 11.—Roentgenogram taken five months later (Oct. 7, 1931) in case 20. The patient's condition is good, with no fever or wheezing. The roentgenogram shows a decrease in the size and density of the hilar shadow. The superior mediastinum is not as wide and the lungs show no definite infiltration.

lobes and also between the right lower and middle lobes. There was a separation of the pleura in the retrosternal region (figs. 9 and 10).

The patient was admitted to the Sea View Hospital on May 17. The wheezing and coughing persisted for about three months, but during this time she gained weight. There was fever for only five days after this admission. When seen in October, 1931, she was in good condition, with dulness in the right upper portion of the chest anteriorly, but no râles were present. Subsequent roentgenograms showed a decrease in the size and density of the hilar shadows. The superior mediastinum was not as wide, and the infiltration gradually cleared up. At present there is no definite infiltration (fig. 11).

V. There were four cases in which, in addition to scattered areas of pulmonary infiltration, a pleural effusion developed during or soon after the measles (nos. 7, 9, 3 and 17). This was usually a serous

effusion from which no organism could be cultivated. In case 7, in which there was an effusion before the measles, a thickened pleura with a small effusion was present after fourteen months.

CASE 9.—R. M., a boy, aged 3 years, a Porto Rican, was admitted to the New York Foundling Hospital on May 2, 1930. He had lived in the same rooms with a relative who had tuberculosis. While he was at the Foundling Hospital his physical examination was normal and there was no fever. Roentgen examination showed enlarged hilar shadows, with a widening of the superior mediastinum. The tuberculin test was positive.

The child was transferred to the Willard Parker Hospital on June 3, 1930; Koplik spots and an early rash were present. Physical examination showed a very sick child with scattered bronchial breathing over the right lung anteriorly and posteriorly; the left lung had only a few râles. Eleven days later there was evidence of fluid at the base of the right lung, and aspiration of the chest yielded a serofibrinous exudate which on culture gave no growth. A roentgenogram taken on admission showed an axillary band which gave a dense shadow along the costal margin of the chest. A roentgenogram taken on June 24 showed the entire right lung to be obscured by a dense opacity. A lateral roentgenogram showed evidence of fluid and an enlargement of lymphatic nodes in front, below and behind the bifurcation of the trachea. The child's general condition became somewhat better, but the physical signs of fluid persisted. While the child was at the Willard Parker Hospital his fever was about 102 F. most of the time.

He was transferred to the Sea View Hospital on Aug. 14, 1930, and continued to have fever. Examination on November 28 showed his general condition to be good, but he was still coughing. Over the right lung anteriorly near the apex there were dulness and amphoric breathing; posteriorly the right lung was still flat. The left lung was clear. The child had gained 6 pounds (2.7 Kg.) in about three months, and since November 15, his temperature had been normal. He was last seen on Oct. 14, 1931, when it was stated that he had gained 5 pounds (2.2 Kg.) in a year. There was no fever. However, physical examination showed diminished breathing and dulness at the base of the right lung posteriorly. Successive roentgenograms showed a gradual absorption of the fluid, and the last one taken, in August, 1931, was interpreted as still showing a thickened pleura with a small amount of fluid.

CASE 17.—E. L., a colored girl, aged 1 year, was admitted to the Nursery and Child's Hospital on June 14, 1929, with a history of having recently recovered from pertussis. There was a history of contact with the grandfather who had recently died of tuberculosis. The patient's general condition was good, and the lungs were clear. A number of roentgenograms of the chest showed enlarged hilar shadows with a widening of the superior mediastinum but no pulmonary infiltrations. The tuberculin test was positive.

The child was admitted to the Willard Parker Hospital on March 30, 1930, because of measles, with fading Koplik spots and a diffuse rash all over the body. A few coarse râles were heard over the chest. The child was never very sick, the temperature being normal six days after admission. The patient was readmitted to the Nursery and Child's Hospital on April 7. Three days later it again had fever, and râles were heard throughout the chest. Soon after admission, roentgenograms of the chest suggested a pleural effusion in the right side of the chest; aspiration on May 11 yielded a clear yellowish fluid.

On May 26, the child was sent back to the Willard Parker Hospital because a positive diphtheria culture was obtained from a membrane on the tonsils. This

membrane disappeared quickly, however, and an examination of the chest still showed evidence of fluid at the base of the right lung. The child's condition rapidly grew worse; fever was present all the time. Roentgenograms showed definite tracheobronchial adenopathy and a pleural effusion. There was hazy mottling in the infraclavicular region, and a lateral examination showed enlarged lymph nodes and a possible effusion in the anterior recess, as manifested by an opacity in the retrosternal region.

The child was transferred to the Nursery and Child's Hospital on June 16, 1931, with signs of meningitis; she died on June 24.

Necropsy showed the right pleural cavity to be studded with tubercles, there being no free fluid. The lymph nodes in the mediastinum were definitely enlarged and caseated. Scattered throughout the parietal and visceral pleurae were fairly numerous pinhead-sized tubercles. The mesenteric lymph nodes were also enlarged and caseated. The right lung was without evident lesion. In the upper lobe of the left lung there was an area of suppuration which suggested a simple acute abscess around which were definite tuberculous lesions. The brain showed a tuberculous meningitis and the cerebellum on section showed a well circumscribed, firm, solitary tubercle about 6 mm. in diameter, located near the midline in the superior portion of the cerebellum and extending practically to the superior surface.

VI. There were cases that, previous to or during measles, showed very little pulmonary infiltration. On lateral exposure, however, enlargement of the lymphatics of the posterior mediastinum and of those localized at the bifurcation could be seen. They were larger and more dense than those seen in measles, in which previous tuberculosis had not been suspected. After the measles these children recovered rapidly and the size of the hilar shadow decreased. There were five cases in this group (nos. 6, 11, 15, 18 and 14).

CASE 6.—N. M., a white girl, aged 2 years, was admitted to the Babies Hospital on Dec. 13, 1929, with a history of a swelling on the right side of the neck for two months. There was no history of tuberculosis in the family. The tuberculin test was positive. The physical examination was normal except for the right cervical adenitis. The glands grew larger and were finally excised on May 29, 1930, there being little fever reaction after the operation. The specimen removed showed typical tuberculous changes. A roentgenogram of the chest showed a moderate increase in the lung markings, with a slight increase in the size of the hilar shadow.

The child was admitted to the Willard Parker Hospital on June 10, 1930, with Koplik spots and an early rash. She was not very sick; there were a few moist râles at the base of the right lung, and the fever returned to normal on June 16. Roentgenograms of the chest showed ill defined opacities scattered through the mesial section of both lungs; there were enlarged hilar shadows and a few calcified nodes in the root structure. The lateral roentgenogram showed enlarged nodes in front, below and behind the bifurcation of the trachea.

The child returned to the Babies Hospital on June 22, the operative incision finally closing on August 20. She did well, there was no fever and a roentgenogram showed no evidence of pulmonary infiltration.

CASE 14.—C. R., a girl, aged 10 months, a Porto Rican, had been at the Metropolitan Hospital before measles developed because there was no one to take care of her at home, the mother having tuberculosis.

The child was admitted to the Willard Parker Hospital on April 8, 1930, because of measles, with Koplik spots and an extensive rash. A few moist râles were heard all over the chest. She was not very sick, and a tuberculin reaction was positive on April 17. During her stay at the Williard Parker Hospital, she had a temperature between 101 and 103 F. every day. Roentgenograms of the chest showed a large dense hilar shadow with pulmonary infiltrations adjacent to the heart shadow. Lateral examination showed dense opacities below, behind and above the bifurcation of the trachea. Before discharge there was a slight retrogression in the hilar regions, but there was confluent mottling at the base of the right lung.

The child was readmitted to the Metropolitan Hospital on April 23. Her fever persisted for a month after readmission. However, the lungs were clear. When she was seen during November, 1930, and April, 1931, her general condition was excellent. Later roentgenograms showed clearing of the pulmonary infiltrations with enlargement of both hilar regions.

It would be valuable, perhaps, if we studied the six fatal cases, in five of which there were necropsies, in a little more detail. In these cases, at least, we can be more certain of our facts. They would show, perhaps, the relationship of measles to the subsequent course of the tuberculosis. The patients died from two weeks to four months after the onset of the measles and were all 2½ years of age or under. Four of them had mild measles. There were five colored children and one white child.

In case 1 the patient had not been very sick before the measles; there had been a discharging sinus from some cervical nodes, and a roentgenogram had shown an enlarged hilar shadow. The child had a relatively mild measles and was ready to be sent home, when it had a rise in temperature, followed by a convulsion, and died in a few days. Postmortem examination showed a generalized miliary tuberculosis, including a tuberculous meningitis. The lungs showed caseating hilar nodes and a diffuse bronchopneumonia with a small caseating tubercle in the apex of the right lower lobe. Microscopically, tuberculous and peribronchial pneumonia were seen. The lymph nodes and the lungs showed evidence of a subacute tuberculous process undergoing rapid necrosis. We feel that the measles caused an extension of the pulmonary tuberculosis with the subsequent miliary process.

In case 2 the patient had been ill for a long time and roentgenograms had shown pulmonary and hilar involvement. The child died eight days after the onset of measles. Postmortem examination showed extensive pulmonary involvement, with evidence of considerable repair and no miliary tuberculosis. Microscopically, this pneumonia was, in the main, nontuberculous. The patient died most probably from measles, with extensive pneumonia.

Case 3 showed a dense shadow in the right lower lobe on admission. The extent of this shadow continued to increase during and after measles until the entire lower lobe was involved. The child finally died

of miliary tuberculosis, including meningitis. The extensive infiltration that this patient had on admission continued to progress until death, necropsy showing no attempt at repair. It is reasonable to suppose that the measles hastened the spread of the tuberculous process.

Data Obtained in Cases of Tuberculosis and Measles

Case	Sex	Color*	Age During Measles	Tuberculosis Suspected Before Measles	Time Followed After Measles	Notes
1	F	N	1 yr.	7 da.	2 wk.	Died of miliary tuberculosis with extensive pulmonary infiltrations
2	F	N	13 mo.	5 mo.	5 da.	Died 5 days after admission with extensive nontuberculous and tuberculous pulmonary infiltration
3	M	N	1 yr.	1 mo.	2 mo.	Died of an extensive pulmonary tuberculosis
4	F	N	2½ yr.	10 mo.	4 mo.	Died of an extensive pulmonary tuberculosis
5	F	W	3 yr.	.....	11 mo.	Fever for several months; then apparently well; roentgenogram still showed infiltration
6	F	W	2 yr.	8 mo.	3 mo.	Tuberculous cervical adenitis; did well soon after discharge
7	M	N	7 yr.	3 wk.	14 mo.	Pleural effusion before measles; some fluid and thickened pleura still present
8	M	W	10 mo.	3 mo.	9 mo.	Lung infiltration present for 10 months; now clear; child doing well
9	M	P	3 yr.	1 mo.	16 mo.	Pleural effusion and pulmonary infiltration after measles; thickened pleura and slight effusion still present
10	M	W	3 yr.	2 mo.	18 mo.	Pulmonary infiltration for several months; at present doing well
11	M	P	2 yr.	3 mo.	2 mo.	Had tuberculous dactylitis; did well soon after discharge
12	M	N	4 yr.	5 mo.	17 mo.	Developed osteomyelitis of spine soon after measles; still in cast
13	F	W	3 yr.	18 mo.	22 mo.	Ill for a long time after measles; at present has phlyctenular conjunctivitis
14	F	P	10 mo.	.....	14 mo.	Fever for one month afterward; now doing well
15	F	W	4 yr.	.....	5 mo.	Did well soon after discharge
16	M	N	2 yr.	.....	1 yr.	Fever for several months after discharge; now doing well
17	F	N	1½ yr.	9 mo.	2½ mo.	Died; autopsy showed caseation of hilar and peritoneal lymph nodes; also meningitis
18	F	W	1½ yr.	2 mo.	2 mo.	Did well soon after discharge
19	M	W	1½ yr.	3 mo.	6 wk.	Died of tuberculous pneumonia and meningitis
20	F	N	1½ yr.	9 mo.	5 mo.	Sick for several months after measles; now doing well

* N, Negro; W, white; P, Porto Rican.

Case 4 showed evidence of pulmonary infiltration and lymph node involvement before the measles. However, with the beginning of the measles the infiltration continued to progress, with evidence of cavitation, the child dying four months after the onset.

In case 17 the patient had no infiltration in the lungs immediately after the measles. Soon after, however, there was evidence of pulmonary infiltration with some fluid in the pleura. This child died two and one-half months later of tuberculous meningitis. Necropsy showed large caseating hilar and mesenteric lymph nodes and a tuberculous

peritonitis. There was little pulmonary involvement. In this case it would seem that the measles reactivated a latent tuberculous process.

In case 19 the patient had dactylitis and, in addition, a small area of consolidation in the right upper lobe before measles. During measles there was further infiltration around this area. The child was discharged in good condition. However, signs of meningitis developed, and necropsy showed small scattered areas of tuberculous pneumonia with caseation at the site of the original infection. Here, too, the measles perhaps activated a tuberculous focus in the process of healing.

We are tempted to believe that the measles hastened the spread of the tuberculosis in at least five of the six cases. In case 2 the patient would probably have died without the tuberculosis. One must admit, however, that without a history of measles a catastrophe, such as a rupture of even a small active tuberculous focus into a blood vessel or lymphatic vessel with a subsequent miliary tuberculosis as in cases 1, 17 and 19, may occur at any time during a tuberculous infection. The extent of the pulmonary involvement was not the only factor in the prognosis. Many of the patients who did not die had extensive pulmonary involvement.

COMMENT

In a previous paper [5a] we reported the observations on successive roentgenograms of the chest of a hundred and thirty children taken during measles. It was shown that shadows suggesting pulmonic infiltration were present in 62.4 per cent of the patients less than 4 years of age and in 42.2 per cent of the patients 4 years of age or over. In the cases showing infiltration, this was present in at least 61 per cent before or during the height of the eruption. The infiltration was often present in cases that were considered clinically mild. Abnormal intensity of the pulmonary markings, pleuropulmonary changes and progressive and retrogressive hilar changes were also present. In an unpublished series of cases of measles without tuberculosis in which lateral as well as postero-anterior exposures were made there was even a greater incidence of pleural and lymphatic involvement. Viethen [8] found similar changes during measles and showed that the infiltrations persisted without any rise in temperature for a long time after the measles, the children making an uneventful recovery.

When fifty-six of our patients [5b] returned for reexamination from six to ten months after the measles, the roentgenograms of the chest were found to be normal except that in many of the cases there was additional pleural involvement.

In the present study we have attempted to ascertain the effect of measles on the pulmonary system of children known to be infected

8. Viethen, A.: Klinische und röntgenologische Lungen Untersuchungen Masernkranken Kinder, Klin. Wchnschr. **10**:2072 (Nov. 7) 1931.

with tuberculosis. Taking roentgenograms during measles and comparing them with those taken before and after measles may give some indication of what actually occurs in the respiratory tract. It is obvious that in such a study as this, one must not draw too rigid conclusions from the roentgen evidence alone. Roentgenographic interpretations are open to error.

Schick [9] has made the following comment, which I believe is worth quoting:

> One is very much tempted to consider all pulmonary infiltrations in children with a positive tuberculin reaction as either tuberculous or epituberculous. Yet, I have frequently seen unresolved lung infiltrations (roentgenologically controlled) simulating tuberculous infiltration in which tuberculous infection has been excluded by every known test. These infiltrations remain weeks and even months in both young and older children. Such infiltration may entirely disappear, then reappear without any evidence of tuberculosis. I must admit, therefore, that even in persons with a positive tuberculin reaction, nonspecific lung infiltrations may occur which have a different prognosis, and as to an ultimate cure, must be considered more favorable than a tuberculous process.

Wessler and Jaches,[10] in their book on clinical roentgenology of the chest, said:

> Extensive tuberculous infiltrations are susceptible to complete resorption with a restitution of the integrity of the lung. It will be recalled that the characteristic product is a sero-cellular exudate in the alveoli, which occurs either alone as an extensive pneumonia or as a zone of exudation about a group of tubercles. Now, it is a matter of common observation that pneumonic exudates do not necessarily go on to caseation but that after a variable period they may undergo partial or complete absorption, depending on the virulence of the toxin.

Bigler,[11] Fleischner [12] and others have found a nontuberculous pneumonia post mortem in patients thought to have had a tuberculous pneumonia. Some roentgenologists believe that if there is a question of both nonspecific and tuberculous diffuse bronchopneumonia in the roentgenogram of a child known to be tuberculous, the foci of uncomplicated bronchopneumonia disappear or change from day to day with astonishing rapidity, while those of tuberculosis prevail for long periods. Many, however, do not concede this fact.

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9. Schick, B., in Engel, S., and Pirquet, C.: Handbuch der Kindertuberkulose, Leipzig, Georg Thieme, 1930, vol. 2, p. 1543.

10. Wessler, H., and Jaches, L.: Clinical Roentgenology of Diseases of the Chest, Troy, N. Y., The Southworth Company, 1923, p. 155.

11. Bigler, J. A.: Interpretation of Roentgenograms of the Chest in Children Based on Observations at Necropsy: II. Tuberculosis, Am. J. Dis. Child. **38:** 1166 (Dec.) 1929.

12. Fleischner, F.: Heilungsvorgange und Heilungsnachweis den Lungentuberkulose in Röntgenbilde, Ergebn. d. ges. Tuberk. **1:**195, 1930.

According to Kochman,[13] the danger of reactivation of a latent process or the spread of an active tuberculous process is apparently not as great in ordinary pneumonia as in pneumonia with measles. He reported five deaths from pneumonia in a large number of children with a positive tuberculin reaction. In only one child did he feel that the tuberculosis contributed to the death. He thought, therefore, that an intercurrent pneumonia has no effect on tuberculosis. He did not give the ages of the patients. Presumably they were young children.

One of the most frequent and characteristic findings in our series was a tremendous enlargement of the hilar shadow with dense, coarse strands radiating out into the lung fields. Wessler and Bass [14] and others believe this reaction to be an exudative inflammatory process in the lung tissue around tuberculous hilar nodes, and call it either recurrent hilar or epituberculous infiltration. It may recur after respiratory diseases.

The immunologic relation between measles and tuberculosis is interesting, and there is a vast literature on this subject. It has been summed up and reviewed recently by Goebel.[15] As is well known, a positive tuberculin reaction becomes negative during measles and usually stays negative until ten days after the appearance of the rash. However, if a tuberculin test is made a few days or even weeks before the onset of measles, a positive reaction becomes intensified during the preeruptive stage. Lukács and Dirner [16] attempted to enhance the growth of the tubercle organism by adding the blood serum of patients with measles to the mediums used. This had no effect, however.

SUMMARY

1. A study was made to ascertain the effect of measles on the pulmonary system of twenty children between the ages of 10 months and 7 years, known to be infected with tuberculosis. Clinical and roentgenographic methods were used before, during and after measles. The cases were followed for a period of from two weeks to twenty-two months.

2. In all, a hundred and seventy-two roentgenograms were studied. In fifteen children, roentgenograms were taken before the measles were obtained. In seventeen children, roentgenograms were taken during the measles and in seventeen cases after the measles had subsided.

13. Kochman, R.: Studien zur Pneumonie im Kindesalter: I. Ueber Beziechungen zwischen Tuberkulose und Lungenentzündung, Arch. f. Kinderh. **91:** 267 (Oct. 21) 1930.

14. Wessler, H., and Bass, M. H.: Recurrent Hilus Infiltration, Am. J. Dis. Child. **11:**198 (March) 1916.

15. Goebel, F.: Der Beeinflussung der Kindertuberkulose durch hinzutretende Infectionen, Ergebn. d. inn. Med. u. Kinderh. **36:**126, 1929.

16. Lukács, J., and Dirner, Z.: Masern und Tuberkulose, Arch. f. Kinderh. **90:**116 (March 28) 1930.

3. The clinical course and the roentgenographic changes in the pulmonary system during and after measles varied. In accordance with these findings the cases were divided into six groups.

4. The patients who died and on whom necropsies were performed are discussed in detail. These patients were 2½ years of age or younger. Five of the six children that died were Negroes.

5. The importance of the interpretation of the roentgenogram of the chest is discussed. One must not draw too rigid conclusions from roentgenographic evidence alone.

6. While we cannot definitely state the effect of measles on tuberculosis, we feel that in young children, judging from clinical, roentgenologic and pathologic findings, measles contributes in many cases to the spread of the tuberculous process.

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EFFECT OF HEAT ON THE ANTIGENIC PROPERTIES OF MILK

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During recent years it has been found that milk sensitization is a relatively common cause of food allergy, and although more frequently observed in infants, it occurs in adults as well. Many of these milk sensitive persons are unable to take raw or pasteurized cow's milk but can well tolerate boiled, evaporated or dried cow's milk. In an endeavor to explain this better tolerance for heated milk, the present study was undertaken.

The chemical and immunologic properties of milk have been extensively studied for many years. A complete review of the literature with a summary of the work done prior to 1921 is given by Wells and Osborne.[1]

From milk, a complex protein-containing solution, four proteins have been isolated, which have been found to be chemically and immunologically distinct. Casein, a complex calcium salt containing phosphorus, occurs in a colloidal form and is readily separated from the whey proteins by the addition of dilute acids. The whey proteins, lactalbumin and lactoglobulin, can readily be "salted out" of the whey solution, and the fourth, the alcohol-soluble protein, is obtained from freshly precipitated casein by extraction with from 50 to 70 per cent ethyl alcohol.

Although casein has no counterpart in serum, the whey proteins are biologically similar to the serum proteins of the animal from which they are derived. This is due to the presence of lactoglobulin, which is serologically related to the serum globulin. Only a small amount of lactoglobulin is present in milk, while larger quantities are present in colostrum, and it is because of its presence that milk at times sensitizes to beef serum. The reaction does not always occur, since

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1. Wells, H. G., and Osborne, T. B.: Anaphylaxis Reactions with the Purified Proteins from Milk, J. Infect. Dis. **29**:200, 1921.

only small amounts are present in milk, and it has been shown by Lewis [2] that when a small amount of antigen has been injected into an animal together with excessive amounts of another antigen, the former may be prevented from manifesting its antigenic activity. Lactalbumin and serum albumin are chemically and immunologically distinct.

Casein has been shown by anaphylaxis tests to be immunologically as distinct from the whey proteins and serum proteins of its own species as it is chemically. A closer biologic and chemical relationship exists between caseins derived from widely different species than between casein, whey and serum proteins of the same species. Although even the delicate method of spectrophotometric comparison of different caseins has shown that they are practically identical, Dudley and Woodman [3] demonstrated by a study of the products of racemization that there are some structural differences. That is, although the caseins from cow's milk and sheep's milk consist of identical amino-acids in apparently identical proportion, when these are racemized, all of the tyrosine and most of the lysine of the sheep's casein remains unracemized, while both are completely racemized in cow's milk. This probably signifies a difference in the position of the amino-acids in the caseins from different species. However, by methods available at the present time, no differences in the antigenic property of caseins from different species have been found.

Casein, after precipitation with acid, can be dissolved without losing its antigenic properties and is fairly active in this respect. The remaining proteins are likewise capable of producing anaphylactic sensitization and shock, lactoglobulin being the most active. Lactalbumin is fairly active, differing in this respect from serum albumin, which is considered somewhat defective in its antigenic properties.[4] The alcohol-soluble fraction, although derived from casein, is not a cleavage product and is a fairly active anaphylactogen.

Observations have been made from time to time on the effect of heat on the immunologic properties of milk and its proteins. An early observer was Moro,[5] who in 1901 noted that heating milk one-half hour at 100 C. did not destroy its reactivity or its antigenic properties.

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2. Lewis, J. H.: Inhibitory Action of Heterologous Protein Mixtures on Anaphylaxis, J. Infect. Dis. **17**:241, 1915.

3. Dudley, H. W., and Woodman, H. E.: Specificity of Caseinogens: Comparative Study of Caseins of Cow and Sheep, Biochem. J. **9**:97, 1915.

4. Dale, H. H., and Hartley, P.: Anaphylaxis to the Separated Proteins of Horse Serum, Biochem. J. **10**:408, 1916.

5. Moro, E.: Biologische Beziehungen zwischen Milch und Serum, Wien. klin. Wchnschr. **14**:1073, 1901.

Fuld,[6] in 1902, stated that boiled milk and sterilized milk react just as well against antiserums as raw milk, and that heated milk or casein solutions do not produce precipitins, but the latter statement has been shown to be incorrect. That the anaphylactogenic activity of casein solution is not materially impaired by heat, was shown by Wells [7] in 1908 by the use of solutions of casein heated at 100 C. for twenty-five minutes. In 1914, Kudicke and Sachs [8] found that although anti-milk serum will, under suitable conditions, give complement-fixation reactions with homologous blood serum, this reaction will not occur if the antiserum for boiled milk is used. Versell,[9] in 1916, observed that antiserums obtained by injecting boiled milk are much less active than antiserums for fresh milk; that boiled milk and boiled milk constituents react less with all antiserums than unboiled; that boiled casein gives some reactions but boiled whey does not, and that the antigenic activity of casein and milk decreases as the amount of heat is increased.

In studying the antigenic properties of milk, von Baeyer,[10] in 1928, found that antiserums for raw goat's milk react better with raw goat's milk than with goat's milk heated one-half hour at 100 C., and antiserums for goat's milk heated at 100 C. are less strong than those for raw milk but react better with raw milk than with boiled milk.

In order to determine whether or not the proteins of milk were altered during the process of evaporation in preparing commercial evaporated milk, Cutler [11] studied the antigens before and after evaporation by means of sensitization tests. He found that there were no quantitative differences in the anaphylactic response to caseins derived from pasteurized and evaporated milk, but there was an alteration in the whey proteins during the process of heating. The quantity of soluble protein available from whey of evaporated milk was always less than half that obtained from raw or pasteurized milk, as determined by the Kjeldahl process. Also, the heating involved in the preparation of evaporated milk altered the immunologic properties of the whey proteins so that the minimum lethal dose was larger than that

6. Fuld, E.: Ueber das Bordetsche Laktoserum, Beitr. z. chem. Phys. u. Path. **2**:425, 1902.

7. Wells, H. G.: Studies on the Chemistry of Anaphylaxis, J. Infect. Dis. **9**:147, 1911.

8. Kudicke, R., and Sachs, H.: Ueber das biologische Verhalten roher und gekochter Milch, Ztschr. f. Immunitätsforsch. u. exper. Therap. **20**:316, 1914.

9. Versell, A.: Ueber das serologische Verhalten von Milch und Milcheiweisskörpern in frischem und gekochten Zustande, Ztschr. f. Immunitätsforsch. u. exper. Therap. **24**:267, 1916.

10. von Baeyer, E.: Zur Kenntnis der Antigenfunktionen der Milch, Ztschr. f. Immunitätsforsch. u. exper. Therap. **56**:241, 1928.

11. Cutler, O. I.: Antigenic Properties of Evaporated Milk, J. A. M. A. **92**:964 (March 23) 1929.

of the whey proteins from either raw or pasteurized milk. There was a greater reactivity of heated whey proteins in animals sensitized with heated milk, but no differences were noted with the casein. Similar results were obtained by the precipitin and complement-fixation tests.

The present study was undertaken to compare, by means of the complement-fixation test, the antigenic properties of raw, pasteurized, evaporated and Smaco 303 milks, and to ascertain the effect of heat on the antigenic properties of raw milk, casein derived from raw milk and the whey proteins from raw milk. Evaporated milk was used as an example of cow's milk heated to a high temperature for a short period of time (240 F. or 116 C. for fifteen minutes), and, because of the reduction in its volume to one-half during the process of evaporation, it was diluted 1 : 1 with physiologic solution of sodium chloride. Smaco 303, so-called hypo-allergic fat-free milk, made by the S. M. A. corporation, was used as an example of milk heated to a lower temperature for a longer period of time. The exact details of the latter process are not available; however, Smaco 303 seems closely to resemble milk that has been refluxed at its boiling temperature for a period of from four to five hours.

Antiserums were prepared by immunizing groups of two rabbits each to raw,[12] pasteurized, evaporated (diluted 1 : 1) and Smaco 303 milks, respectively; and the antigens consisted of raw, pasteurized, evaporated (1 : 1) and Smaco 303 milks; casein and whey proteins prepared from each, and raw milk and the casein and whey proteins from raw milk heated at temperatures varying from 60 to 120 C. for one hour.

Casein was prepared by the Van Slyke-Baker method,[13] the precipitant used being lactic acid. The alcohol-soluble protein was removed from the casein by extraction with 70 per cent alcohol. As the individual whey proteins were not isolated, the filtrate after the removal of casein was neutralized with sodium hydroxide and used as such. Protein determinations, by means of trichloracetic acid, were made on each antigen before each test was performed, so that equal amounts of protein were used. The antigenic activity of the various types of milk was compared by means of the complement-fixation test, by titrating the various types of milk with various antiserums. All milks, either when used as such or as a source of the different preparations, were centrifugated to remove the butter fats and other solids.

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12. Raw milk was obtained from dairies and is known to the trade as "certified" milk.

13. Van Slyke, L. L., and Baker, J. C.: Preparation of Pure Casein, J. Biol. Chem. **35**:127, 1918; Method for Making Electrometric Titration of Solutions Containing Protein, ibid. **35**:137, 1918.

In table 1 are given the results of experiments made on the reaction of the four types of antiserums with four types of whole milk. With the antiserum for raw milk, the raw milk reacts in the highest dilution.[14] There is little or no difference in the reactivity of pasteurized or evaporated milks, although both of them are less reactive than raw milk, and they, in turn, are more reactive than Smaco. With antiserums for pasteurized milk, a distinct difference is demonstrated between the milks heated to high temperatures (evaporated and Smaco) and those heated either to low temperatures or not at all (raw and pasteurized). With antiserums for evaporated milk, the difference between the reac-

TABLE 1.—*Reactions of Various Milks with Different Milk Antiserums* *

	Milligrams Protein											
	0.025	0.015	0.010	0.005	0.0025	0.0015	0.0010	0.0005	0.00025	0.00015	0.00010	0.00005
Antiserum for Raw Milk†												
Raw milk	0	0	0	0	0	0	0	2	2	4	4	4
Pasteurized	0	0	0	0	0	0	0	4	4	4	4	4
Evaporated	0	0	0	0	0	1	2	4	4	4	4	4
Smaco	0	0	0	0	0	2	4	4	4	4	4	4
Antiserum for Pasteurized Milk												
Raw milk	0	0	0	0	0	0	0	0	4	4	4	4
Pasteurized	0	0	0	0	0	0	0	0	4	4	4	4
Evaporated	0	0	0	0	4	4	4	4	4	4	4	4
Smaco	0	0	0	0	4	4	4	4	4	4	4	4
Antiserum for Evaporated Milk												
Raw milk	0	0	0	0	0	0	0	0	0	2	3	4
Pasteurized	0	0	0	0	0	0	3	4	4	4	4	4
Evaporated	0	0	0	0	0	0	0	4	4	4	4	4
Smaco	0	0	0	0	0	3	4	4	4	4	4	4
Antiserum for Smaco Milk												
Raw milk	0	0	0	0	0	0	0	0	4	4	4	4
Pasteurized	0	0	0	0	0	0	0	0	2	3	4	4
Evaporated	0	0	0	0	0	4	4	4	4	4	4	4
Smaco	0	0	0	0	3	4	4	4	4	4	4	4

* 0, no hemolysis; 4, complete hemolysis; 1, 2 and 3, varying degrees of hemolysis between 0 and 4.

† The titers of the different antiserums cannot be compared with each other as serums from different animals vary in antibody content.

tivity of pasteurized and evaporated milks is not in evidence, but the inferiority of Smaco as an antigen is again seen. With the anti-Smaco serum, better reactions were obtained with pasteurized milk than with raw, a fact that was repeatedly observed. Again, evaporated milk and Smaco reacted less than pasteurized and raw milk. It seems from these experiments that the milks are decreased in antigenic reactivity according to the degree to which they are heated, and that this difference is increased or decreased according to the specificity of the antiserum used. The latter fact gives support to the claims that heating alters some antigens, in that they give rise to antiserums that are more or less specific for the heated antigens, the so-called cocto-antigens.[15]

14. Complete hemolysis is taken as the end-point.

15. Furth, J.: Antigenic Character of Heated Proteins, J. Immunol. **10**:777, 1925.

In table 2, the results of the titration of the individual preparations of casein with the individual antiserums are given. The results are similar to those given in table 1 but are more definite, although there is less evidence that specific antibodies are formed for the heated casein. It is seen that casein derived from raw and pasteurized milk is more highly antigenic than that derived from evaporated milk and Smaco. Although casein is relatively heat-stable, it is observed that it suffers a decrease in antigenic activity when heated sufficiently long or to a sufficiently high temperature. However, it is probable that, although the caseins were prepared by identical procedures, heat-coagulable proteins were present to contaminate the caseins from evaporated milk

TABLE 2.—*Reactions of Various Caseins with Different Milk Antiserums*

	Milligrams Protein									
	0.01	0.006	0.004	0.002	0.001	0.0006	0.0004	0.0002	0.0001	0.00006
Anticertified Milk Serum										
Casein from:										
Raw milk.....	0	0	0	0	0	0	1	2	4	4
Pasteurized.....	0	0	0	0	0	0	0	2	4	4
Evaporated....	0	0	0	0	2	4	4	4	4	4
Smaco.....	0	0	1	4	4	4	4	4	4	4
Antipasteurized Milk Serum										
Casein from:										
Raw milk.....	0	0	0	0	0	0	2	4	4	4
Pasteurized.....	0	0	0	0	0	0	2	4	4	4
Evaporated....	0	0	1	3	4	4	4	4	4	4
Smaco.....	4	4	4	4	4	4	4	4	4	4
Anti-Evaporated Milk Serum										
Casein from:										
Raw milk.....	0	0	0	0	0	0	0	0	0	1
Pasteurized.....	0	0	0	0	0	0	0	0	0	1
Evaporated....	0	0	0	0	1	2	3	4	4	4
Smaco.....	0	0	0	3	4	4	4	4	4	4
Anti-Smaco Milk Serum										
Casein from:										
Raw milk.....	0	0	0	0	0	0	0	0	0	4
Pasteurized.....	0	0	0	0	0	0	0	0	2	4
Evaporated....	0	0	0	0	0	0	4	4	4	4
Smaco.....	0	0	0	0	3	3	4	4	4	4

and Smaco. The effects of varying degrees of heat on the reactivity of raw casein are shown later.

Table 3 represents the results of the titration of the various whey proteins with the various antiserums. In these experiments it was necessary to adjust the doses of the different wheys used in order that they would contain similar amounts of protein, since it was found that the amount of protein in solution after the precipitation of casein varied markedly between raw and pasteurized milks on one hand and evaporated and Smaco milks on the other. The weights of protein obtained by precipitation with trichloracetic acid from 50 cc. of each type of whey were, for example, raw, 0.4079 Gm.; pasteurized, 0.4904 Gm.; evaporated, 0.2709 Gm., and Smaco, 0.2110 Gm. When these differences were adjusted so that complement-fixation experiments were

made in each case with comparable amounts of proteins, it is seen that the wheys from evaporated milk and Smaco are more active antigenically than those from raw and pasteurized milks, and that again these differences are large or small, depending on the type of antiserum used. No explanation of the enhanced activity of the heat-stable whey proteins can be offered. That such an increased activity is real is indicated by the consistency of the evidence in all experiments with the four types of antiserums, and by the fact the differences are large.

In order to study the changes induced by heat in milk, samples of 20 cc. each of raw milk, casein prepared from raw milk and the whey

TABLE 3.—*Reactions of the Various Wheys with Different Antiserums*

	Milligrams Protein											
	0.730	0.438	0.292	0.146	0.0730	0.0438	0.0292	0.0146	0.00730	0.00438	0.00292	0.00146
Anticertified Milk Serum												
Raw milk	0	0	0	0	0	1	2	3	4	4	4	4
Pasteurized	0	0	0	0	0	0	0	1	3	4	4	4
Evaporated	0	0	0	0	0	0	0	0	0	1	3	4
Smaco	0	0	0	0	0	0	0	0	2	3	4	4
Antipasteurized Milk Serum												
Raw milk	0	0	0	0	0	0	2	4	4	4	4	4
Pasteurized	0	0	0	0	1	1	3	4	4	4	4	4
Evaporated	0	0	0	0	0	0	0	1	2	3	4	4
Smaco	..	..	..	..	..	2	2	2	4	4	4	4
Anti-Evaporated Milk Serum												
Raw milk	0	0	0	0	0	0	0	2	4	4	4	4
Pasteurized	0	0	0	0	0	0	0	0	3	4	4	4
Evaporated	0	0	0	0	0	0	0	0	0	0	3	4
Smaco	0	0	0	0	0	0	0	0	1	2	3	4
Anti-Smaco Serum												
Raw milk	0	0	0	2	3	4	4	4	4	4	4	4
Pasteurized	1	1	3	3	4	4	4	4	4	4	4	4
Evaporated	0	0	0	0	0	0	0	0	0	0	1	4
Smaco	0	0	0	0	0	0	0	0	0	1	2	4

proteins from raw milk were sealed in ampules and heated to 60, 80 and 100 C. for one hour in an oil bath.

Macroscopically, little change was noted in raw milk when heated until the temperature was elevated to 110 C. At this point there was a slight color change (ivory color); at 120 C., the color change was more marked and might be described as resembling "café au lait," and at 140 C., there was a marked disintegration, a heavy, pale brown flocculent precipitate settling to the bottom of the ampule with a clear, yellow-brown serum-like fluid above it. The precipitate in the latter ampule was emulsified as much as possible, and the mixture used as such. Complement-fixation tests were made with each preparation, an antiserum for raw milk being used. The results are seen in table 4. It is observed that no change occurs until the temperature exceeds 110 C., when there is a marked decrease in antigenic activity. This represents the approximate temperature to which evaporated milk is heated

for a period of fifteen minutes for purposes of sterilization (i. e., 240 F. or 116 C.). Thus, it is seen that whole milk does undergo slight changes in antigenic activity when subjected to heat.

Casein from raw milk made up in a 1 per cent solution, dissolved at p_H 7.0, was heated in sealed ampules in the foregoing manner. After heating, even less macroscopic change was noted than in the case of milk, since only at 120 and 140 C. was there a very fine, white flocculent precipitate. The results of the complement-fixation tests shown in table 5 are similar to the preceding ones obtained with heated whole milks, as no change is noted until a temperature of 110 C. is reached, and then there is a slight decrease in antigenic activity, which becomes more marked at 120 C.

TABLE 4.—*Effect of Heat on the Antigenic Reactivity of Whole Milk with Antiserum for Raw Milk*

	Cubic Centimeters											
	0.005	0.003	0.002	0.001	0.0005	0.0003	0.0002	0.0001	0.00005	0.00003	0.00002	0.00001
Raw milk unheated.....	0	0	0	0	0	0	0	0	0	0	0	4
Raw milk heated 1 hour at 60 C.	0	0	0	0	0	0	0	0	0	0	0	4
Raw milk heated 1 hour at 80 C.	0	0	0	0	0	0	0	0	0	0	0	4
Raw milk heated 1 hour at 100 C.	0	0	0	0	0	0	0	0	0	0	0	4
Raw milk heated 1 hour at 110 C.	0	0	0	0	0	0	0	0	0	0	0	4
Raw milk heated 1 hour at 120 C.	0	0	0	0	0	0	0	0	2	4	4	4

TABLE 5.—*Effect of Heat on the Antigenic Reactivity of Casein with Antiserum for Raw Milk*

	Milligrams Protein											
	0.10	0.07	0.05	0.02	0.01	0.007	0.005	0.002	0.001	0.0007	0.0005	0.0002
Raw milk casein.....	0	0	0	0	0	0	0	0	0	4	4	4
Raw milk casein heated 1 hour at 60 C.	0	0	0	0	0	0	0	0	4	4	4	4
Raw milk casein heated 1 hour at 80 C.	0	0	0	0	0	0	0	0	4	4	4	4
Raw milk casein heated 1 hour at 100 C.	0	0	0	0	0	0	0	0	4	4	4	4
Raw milk casein heated 1 hour at 110 C.	0	0	0	0	0	0	0	4	4	4	4	4
Raw milk casein heated 1 hour at 120 C.	0	0	0	0	4	4	4	4	4	4	4	4

The whey proteins from raw milk were heated at p_H 7.0 in the foregoing manner. Here the results are much more definite and striking, both macroscopically and as shown by the complement-fixation test. Even when heated to 60 C. for one hour, a slight, fine, white flocculent precipitate becomes progressively more marked, so that at 120 C. it is coarse and curdlike. At 140 C., color changes are noted in that the precipitate becomes sand-colored and there is a distinctly yellow supernatant fluid. The results obtained from the complement-fixation test are striking, since even at 60 C. a definite decrease in antigenic activity is observed (see table 6), which becomes progressively more marked as the temperature is increased. Thus, whey proteins are seen to be extremely heat-labile and suffer a progressively more marked reduction in antigenic activity as the temperature is increased.

Milk plays an important part in the production of allergic manifestations, particularly in infants and children. According to Coca, Walzer and Thommen,[16] it is the third most common food offender, eggs and wheat ranking first and second. The degree of sensitization and the type of symptoms produced vary greatly, and it has been found by means of skin tests and elimination diets that many chronic allergic conditions are due to such a sensitization and are relieved by the removal of this protein from the diet (Rowe,[17] Ratner,[18] etc.). In all but the more severe forms, milk which has been boiled, superheated or dried is usually well tolerated. To what exent this better tolerance depends on the denaturation of proteins and to what exent on the greater ease of digestibility is difficult to determine. It has been shown by Wallen-Lawrence and Koch [19] that raw milk when pasteurized, boiled or evaporated undergoes changes that make it more readily digested

TABLE 6.—*Effect of Heat on the Antigenic Reactivity of Whey Proteins with Antiserum for Raw Milk*

	Cubic Centimeters											
	0.05	0.03	0.02	0.01	0.005	0.003	0.002	0.001	0.0005	0.0003	0.0002	0.0001
Raw milk whey	0	0	0	0	0	0	0	1	3	4	4	4
Raw milk whey heated 1 hour at 60 C.	0	0	0	0	0	0	2	4	4	4	4	4
Raw milk whey heated 1 hour at 80 C.	0	0	0	0	2	4	4	4	4	4	4	4
Raw milk whey heated 1 hour at 100 C.	0	0	1	4	4	4	4	4	4	4	4	4
Raw milk whey heated 1 hour at 110 C.	1	2	3	4	4	4	4	4	4	4	4	4
Raw milk whey heated 1 hour at 120 C.	3	3	4	4	4	4	4	4	4	4	4	4
Raw milk whey heated 1 hour at 140 C.	4	4	4	4	4	4	4	4	4	4	4	4

by trypsin in vitro, the changes being quantitative in proportion to the amount of heat applied and the length of time heated. Since no change is noted in the digestibility of casein after prolonged heating, it is assumed that the increase in digestibility is due to a change in some heat-labile constituent of the whey. In the digestion of heated milks it is possible that the milk proteins are reduced to harmless constituent amino-acids which when absorbed are not toxic, whereas, in the digestion of raw milk, the process does not go on to completion, and intermediate products are formed which are toxic to sensitized persons, or which are large enough molecules to act as antigens when absorbed.

16. Coca, Walzer and Thommen: Asthma and Hay Fever in Theory and Practice, Springfield, Ill., Charles C. Thomas, 1931, p. 426.

17. Rowe, A. H.: Food Allergy, Philadelphia, Lea & Febiger, 1931, p. 359.

18. Ratner, B.: Eczema in Infancy Due to Protein Sensitization, M. Clin. North America **9**:817, 1925.

19. Wallen-Lawrence, Z., and Koch, F. C.: The Relative Digestibility of Unsweetened Evaporated Milk, Boiled Milk and Raw Milk by Trypsin in Vitro, Am. J. Dis. Child. **39**:18 (Jan.) 1930.

SUMMARY

1. By means of complement-fixation tests, it has been shown that the serologic reactivity of whole raw and pasteurized milks is greater than that of evaporated milk and Smaco 303, but that this difference varies in the presence of specific antiserums.

2. Casein derived from pasteurized and raw milks reacts in a higher dilution with all antiserums than casein derived from evaporated and Smaco 303 milks.

3. There is a slight increase in the reactivity of equal amounts of whey proteins derived from evaporated and Smaco 303 milks. The increase in reactivity is more apparent in the tests made with antiserums for evaporated and Smaco milks.

4. The isolated whey proteins from raw milk are extremely heat-labile, since there is a decrease in antigenic reactivity even at 60 C., which becomes progressively more marked as the temperature is increased.

5. Casein derived from raw milk is relatively heat-stabile, no change being noted in its antigenic reactivity until the temperature exceeds 100 C.

6. Raw milk is relatively heat-stabile, since little change occurs in its antigenic activity until the temperature exceeds 110 C., probably because milk is composed chiefly of casein and because the casein protects to some extent the effect of heat on the whey proteins.

7. There is some evidence that immunization with heated milks produces antiserums that are relatively specific for the heated proteins of milk.

SOY BEAN (VEGETABLE) MILK IN INFANT FEEDING

PRELIMINARY REPORT

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While the use of the soy bean (Glycine hispida) as a source of human food is comparatively new in this country, it has, for many centuries, occupied a prominent place in the dietary of the Orient. In China it represents a large part of the food consumption, and in Japan, Korea, Indo-China, Siam, the Philippines, the Dutch Indies and India it has been extensively used for many years.

A product of early cultivation in China, its use dates back to the beginning of China's agricultural age under the Emperor Shen Nung. It is mentioned in the ancient "Materia Medica" (Ben Tsao Gang Mu) written in 2838 B. C. Although the Chinese consume but small quantities of meat and dairy products, they have been able to elaborate well balanced, adequate diets by the use of the soy bean. The importance of this food in the Chinese dietary is further emphasized in the statistics mentioned by Horvath: [1]

In recent years great interest in the study and use of soy bean preparations has been manifested throughout the world.[2] Prominent forces in this country are the Bureau of Home Economics and W. J. Morse of the United States Department of Agriculture. Von Noorden in Germany, Ducceschi in Italy and Berczeller in Vienna are giving their support to the use of the soy bean as a source of food. Neumann, director of the Hygiene Institute in Hamburg, has made a study of the

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1. Horvath, A. A.: The Soybean as Human Food, Bureau of Industrial and Commercial Information, The Ministry of Industry, Commerce and Labor and the National Government of the Republic of China, Pekin, 1926, ser. 3.

In 1921 China produced 80 per cent of the world's soy bean production, 70 per cent of the latter being harvested in Manchuria. The 1921 crop of soy bean in Manchuria was approximately 4,500,000 tons. The total acreage of the bean in the three provinces was 8,000,000 acres, covering 25 per cent of the cultivated area.

2. Horvath, A. A.: The Soybean as Human Food, Indust. & Engin. Chem. **9**:136 (May 10) 1931.

problem of the soy bean as a food and has contributed many enlightening publications. At the University of Vienna, Durig and Wastl are making studies on the soy bean, and in Russia soy bean foods have become important factors in the national dietary. From the progress made in these and in other investigations, it seems not at all improbable that the soy bean will eventually become a significant part of the dietary in this country. In this connection Horvath,[2] an international authority on the soy bean, said:

> There are reasons to expect that the United States will become the leader in introducing the soybean in the daily diet of the white race. An important step should be the establishment of a soya foundation in order to promote the creation of a national soya food research institute.

While in Europe and in this country the soy bean has been used chiefly in the form of salad oil, a substitute for lard, beef extract, etc., the use of soy bean "milk" as an infant food has been demonstrated. The value of this milk is well known in China. Ruhräh,[3] one of the pioneer investigators on the merits of the soy bean in infant feeding, made a preliminary report in 1909 before the American Pediatric Society. He reported a series of cases in which a gruel, made from the soy bean flour, was used in summer diarrheas and certain forms of intestinal disturbances. He mentioned also its value as a diluent for cow's milk, and as a means of raising the protein in condensed milk. Each ounce of the flour contained 13 Gm. of protein, with a caloric value of 120. In later reports,[4] he mentioned the use of soy bean gruel with condensed milk. In summarizing his six years of experience with the soy bean, he stated that it will not produce rickets or scurvy, and permits a perfectly normal development as far as bones are concerned, and that in successful feeding the infants look like breast-fed babies.

Sinclair,[5] in 1916, reported his results in a series of seventy-four cases of summer diarrhea. In forty-four (59.4 per cent) cases the babies did well. Recently Hill and Stewart [6] have used a soy bean preparation in the feeding of infants sensitized to cow's milk, claiming good results in many cases.

Soy bean milk as a definite food for babies has not, in the past, received serious consideration in this country. In China, however, it has been demonstrated that this vegetable milk can be successfully employed as a food for growing infants. Economic stress and the rela-

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3. Ruhräh, John: The Soy Bean in Infant Feeding: Preliminary Report, Arch. Pediat. **26**:496, 1909.

4. Ruhräh, John: The Soybean as an Article of Diet for Infants, J. A. M. A. **54**:1664 (May 21) 1910; Soybean and Condensed Milk in Infant Feeding, Am. J. M. Sc. **150**:502, 1915.

5. Sinclair, J. F.: Soybean in Infant Feeding, New York State J. Med. **16**:83 (Feb.) 1916; abstr., J. A. M. A. **66**:841 (March 11) 1916.

6. Hill, L. W., and Stewart, H. C.: Soybean Food Preparation for Infants with Milk Idiosyncrasies, J. A. M. A. **93**:985 (Sept. 28) 1929.

tively small consumption of dairy products in China are important factors in the promotion of the soy bean as a food substitute for cow's milk.

Tso [7] made a study of six Chinese infants fed on soy bean milk. His preparation, made from water-soaked soy beans, contained 4.4 per cent protein, 1.8 per cent fat, 1.5 per cent carbohydrate, 0.018 per cent calcium, 0.057 per cent phosphorus and 0.41 per cent total ash; in the diet built on this basis, the proteins constituted from 20 to 22 per cent of the caloric intake. Fifty per cent of the total calories were obtained from this "milk," the supplementary food being cane sugar, corn or rice starch, cod liver oil, calcium lactate, sodium chloride and cabbage water, the latter as the chief source of vitamin C. This mixture was well utilized and proved to be biologically complete.

The infants, one from birth and the others when a few weeks old, were successfully fed from six to nine months on this diet. Their weight curves followed closely the average weight curves of healthy, nursing infants in the United States as well as the average weights of several hundred breast-fed Chinese infants. Their mental and muscular development and nutritional status in general appeared to be as good as one sees in normal infants reared on milk diets.

In an earlier publication, Tso [8] reported his observations on an infant fed soy bean milk for a period of eight months. The supplementary foods consisted of cane sugar, cod liver oil, orange juice, egg, rice porridge, spinach purée and sodium chloride. In spite of the marked deficiency of calcium in this diet and the occurrence of rickets, the infant grew 20.7 cm. and gained 4.1 Kg. in weight, comparing favorably with the average development of breast-fed infants. In his discussion, Tso said:

> This experiment is perhaps the first demonstration that an infant can be successfully fed through the perilous period of the first two months of life on a diet which contains no mammalian milk.

More recently Lane [9] has shown, in an interesting report, that it is possible to feed infants adequately on a vegetable "milk" diet, excluding human and cow's milk. Her report concerns the development of twins (boy and girl) whose mother, during pregnancy, was fed an exclusive vegetable diet. They were nursed for three months, plus a lactic acid supplement. At 3 months a vegetable milk (almond milk) replaced the supplementary feedings of cow's milk, and after the fifth month was used exclusively. The "milk" was made with unbleached almonds, corn

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7. Tso, Ernest: A Vegetable Milk Substitute for North China, Am. J. Physiol. **90**:542 (Oct.) 1929.

8. Tso, Ernest: The Development of an Infant Fed Eight Months on a Soybean Milk Diet, Chinese J. Physiol. **2**:33, 1928.

9. Lane, Dorothy: The Nutrition of Twins on a Vegetable Diet During Pregnancy, the Nursing Period and Infancy, Am. J. Dis. Child. **42**:1384 (Dec.) 1931.

starch, shorts, whole wheat, unroasted peanut flour and soy bean flour. Cod liver oil and fruit juices were given during the period of the experiment. Both infants did well nutritionally; there were no digestive upsets; they slept well and had good appetites, and they showed normal calcification of bone. In addition, they had good resistance against infection. Three physical examinations at varying intervals, up to the age of 27 months, showed normal development in all respects.

This report is of especial significance in connection with our work with the soy bean. Lane included in the dietary of the twins additional food supplements. We, on the other hand, have observed results with the almost exclusive substitution of a vegetable (soy bean) milk for cow's milk.

The mass production, nutritional availability and economic features of the soy bean have prompted us to investigate further its comparative value as a prophylactic infant food. We submit, in this preliminary communication, the results in a series of fifty infants fed soy bean milk alone or as a complement to breast milk, with the addition of substances in which the bean is deficient. Our observations cover a period of one year and the cases here reported are only part of the total number being fed this "milk." Before detailing our results, however, the following facts concerning the soy bean are perhaps necessary for a better understanding of its merits as an infant food.

THE SOY BEAN

This legume is notable for its high protein content, for the presence of vitamins A, B and a small amount of D and for the practically complete absence of starch. The mammoth yellow variety used in our study, which is being used in the manufacture of soy bean milk and flour, has the following composition when dried:

	Tennessee Agricultural Station, Percentage	Harshaw Laboratory, Percentage
Moisture	7.49	7.00
Protein	32.99	40.50
Fat	21.03	18.50
Nitrogen-free extract	29.36	.....
Fiber	4.12	.....
Ash	5.01	.....

The protein has been shown to be adequate for complete maintenance and growth in animals, provided the proper salts are added to bring the salt balance to normal. The amino-acids of the protein are similar to those obtained from the casein of milk (table).

Carbohydrates.—The carbohydrates of the soy bean are entirely free from starch when the bean is mature. A small amount of cane sugar and a slight trace of reducing sugars are present. Most of the carbo-

hydrate is present as galactans, pentosans and insoluble celluloses. Obviously, for purposes of infant feeding, it is necessary to add the proper mixture of sugars.

Fats.—The soy bean fat or oil is liquid at room temperature and contains a high percentage of unsaturated acids. It contains, according to Matthes and Dahle,[10] 15 per cent of palmitic acid and 80 per cent of liquid acids. The latter consist of 70 per cent of oleic acid, about 24 per cent of linolic acid and about 6 per cent of linolenic acid. The unsaponifiable matter contains about 55 per cent of a crystalline portion

Comparison of Amino-Acids in Casein of Cow's Milk and Protein of the Soy Bean

Amino-Acids	Cow's Milk Casein (Foreman, 1916), Percentage	Soy Bean-Protein (Osborne and Clapp, 1907), Percentage
Alanine	1.85	Not isolated
Valine	7.93	0.63
Leucine	9.70	8.45
Proline	7.64	3.78
Phenylalanine	3.88	3.86
Aspartic	1.77	3.98
Glutamic	21.77	19.46
Serine	0.50	Not isolated
Tyrosine	4.50	1.86
Arginine	3.81	5.12
Histidine	2.50	1.39
Lysine	7.62	2.70
Ammonia	1.61	2.56
Tryptophan	1.50 (color, 2.20)	Present (color, 1.66)
Glycine	0.45	1.00
Cystine	..... (color, 0.26)	..... (color, 1.12)

consisting of 2.4 per cent of stigmasterol with a melting point of 139 C. Regarding its iodine absorption value, the figures range from 121 to 141.

Soy beans contain about 1.64 per cent of lecithin-phosphoric acid exactly like that of eggs, so that this plant surpasses others in lecithin content.

Ash.—The soy bean ash contains the following percentages of important chemical elements, calculated to the weight of the dry bean:

Potassium	2.095
Sodium	0.380
Calcium	0.230
Magnesium	0.244
Sulphur	0.444
Chlorine	0.025
Phosphoric acid	0.649

10. Matthes, H., and Dahle, A.: Ueber Sojabohnenöl, Arch. d. Pharm. **149**: 424, 1911.

Tso,[11] comparing the nutritive properties of soy bean milk and cow's milk, stated that the proteins of the soy bean, when fed at a high level of intake, are comparable to those of cow's milk. At the level of 22 per cent of caloric intake, the proteins of the soy bean are slightly superior, and at the 14 per cent level of intake are slightly inferior to those of cow's milk fed at the level of 11 per cent of caloric intake. The addition of calcium, sodium and chlorine to soy bean milk is sufficient to make its salt content comparable to that of cow's milk. In previous experiments he found that without the addition of a calcium salt young rats failed to grow.

Daniel and Hutton [12] found that rats fed exclusively on cow's milk seldom reproduced, and only a small percentage of the young born survived. They explained this by the fact that milk appears to be low in certain inorganic substances necessary for the production of a new generation. The addition of from 7 to 10 Gm. of soy bean powder to 1 liter of the milk was effective in correcting this deficiency. The ash of the soy bean served the same purpose.

Horvath,[13] in a study of the blood calcium in rabbits fed a diet of raw, soaked, yellow soy beans, contradicted the reputed calcium deficiency of the bean. He stated that the yellow soy bean is not deficient in calcium, but that it contains an excess of fat in regard to the calcium-fat ratio required for optimal absorption and metabolism of calcium salts. He concluded that raw, soaked soy beans can restore a lowered blood calcium caused by bleeding in rabbits.

Vitamins.—The soy bean has been found to contain vitamin A in amounts comparable to that in cow's milk, but is much richer in vitamin B. The vitamin content of this bean can best be demonstrated by the following assay. (The quantitative determination of vitamins A, D and B "complex" in the soy bean milk [14] used in this investigation was made experimentally by Dr. Harry Goldblatt, Department of Pathology, Western Reserve University.) A summary of his findings follows:

Vitamin A: For the quantitative determination of vitamin A in soy bean milk, the unit adopted was the least amount of the soy bean milk powder required daily to promote an average gain of 3 Gm. a week for eight weeks, after the end of the usual "depletion" period (Sherman unit). The "depletion" period is the time during which the rats are kept on the otherwise complete diet, deficient in vitamin A, until the gain of weight has definitely ceased.

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11. Tso, Ernest: A Comparison of the Nutritive Properties of Soy-Bean "Milk" and Cow's Milk, Chinese J. Physiol. **3**:353, 1929.

12. Daniels, Amy, and Hutton, Mary: Mineral Deficiencies of Milk as Shown by Growth and Fertility of White Rats, J. Biol. Chem. **63**:143, 1925.

13. Horvath, A. A.: Soybean Feeding and Blood Calcium, Jap. M. World **8**:1 (Jan. 15) 1928.

14. The soy bean milk powder was supplied by Harshaw Essential Foods, Inc., Cleveland.

The tests showed that 0.05 Gm. of the soy bean milk powder was the least amount that satisfied the requirements for a unit of vitamin A. Therefore, 1 ounce (28.3 Gm.) of the soy bean powder contained 560 units of Vitamin A.

Vitamin D: For the quantitative determination of vitamin D in the soy bean milk, the unit of vitamin D adopted was the least amount of the soy bean milk powder required in ten days to induce definite healing of rickets in that period (positive line test) in rats on the Steenbock diet no. 2965. This is the Steenbock unit.

The tests showed that 0.1 Gm. of the soy bean milk powder daily, that is, 1 Gm. in ten days, satisfied the requirements of 1 Steenbock unit. Therefore, 1 ounce of the soy bean milk powder contained 28 Steenbock units of vitamin D.

The tests for vitamin D were performed with soy bean milk powder from which the mineral salts were omitted. This was done to eliminate the antirachitic effect of the inorganic phosphorus contained in the salt mixture. There is some phosphorus in the mixture as it was used, but in the unit dose this was so small as to be negligible. Control tests showed that at least twenty times the amount of phosphorus contained in the unit dose of soy bean milk powder was required to induce by itself a positive line test in ten days. The antirachitic effect of the soy bean milk powder, as shown by the tests, is therefore practically entirely due to its content of vitamin D.

Vitamin B "Complex": For the quantitative determination of vitamin B "complex" (B_1 or F, B_2 or G) in the soy bean milk, the unit adopted was the least amount of powder required daily to induce an average gain of 3 Gm. per week for eight weeks after the end of the "depletion" period (Bourquin unit). The "depletion" period is the time during which the rats are restricted to the diet deficient in vitamin B "complex" but otherwise complete, until gain in weight has definitely ceased. As an additional criterion, signs of the development of polyneuritis were noted.

The tests showed that 1.25 Gm. of the soy bean milk powder satisfied the growth requirements for 1 unit of vitamin B "complex." The rats that received this amount or more showed no signs of polyneuritis. Therefore, 1 ounce of the soy bean powder contained 22 units of vitamin B "complex." Quantitative determinations of vitamin B_1 or F and of vitamin B_2 or G were not made, but the foregoing results show that they were both present.

SOY BEAN MILK POWDER AS AN EXCLUSIVE FOOD FOR ANIMALS

Six rats (three males and three females) were fed the soy bean milk powder and distilled water exclusively. They ate daily from 10 to 20 Gm. of the powder in the form of a thick paste made of 1 part of

soy bean milk powder and 2 parts of distilled water. Four rats were also fed on the soy bean milk powder, but, in addition, every rat received daily 0.5 Gm. of Harris medicinal yeast and 0.05 Gm. of Harris cod liver oil. The rats fed on the soy bean milk powder alone grew as well as those that received the supplement of yeast and cod liver oil to supply additional vitamins A, B and D (chart 8). Their growth was also just as good as that of another group fed on a diet known to be complete for rats. The number of animals fed exclusively on soy bean milk powder was small, but the results indicate that the quantity of vitamins A, D and B "complex" in the mixture is adequate for the normal growth of rats. Many more animals are being fed exclusively on this mixture, and their growth is being compared with others fed on cow's milk and other known milk foods.

From the foregoing facts it will be seen that while the soy bean compares favorably with human and cow's milk in the protein and fat content and the essential vitamins, the chief deficiencies lie in the carbohydrate and mineral salt balance. In the preparation of the soy bean flour, therefore, we made additions in accordance with these deficiencies. Malt syrup and lactose were used to bring up the sugar, cotton seed oil for the maintenance of an optimal fat content and the so-called *Nemsalz* (glycerophosphates of iron and calcium, lactate of magnesium and the chlorides of sodium and potassium) for the mineral salt deficiency, plus the lactate of calcium. The malt syrup included 69.33 per cent of maltose, 5.35 per cent of dextrins, 22.6 per cent moisture and 1.49 per cent of ash. The ingredients going into each batch of flour consisted of the mammoth yellow soy bean, cotton seed oil, butter fat, cod liver oil, malt syrup, lactose, *Nemsalz* and calcium lactate.

PREPARATION OF THE SOY BEAN MILK FLOUR

Soy beans of the mammoth yellow variety were carefully cleaned, washed, specially treated to remove unpleasant flavors and converted to a milky fluid. To this fluid were added the special sugars, mineral salts and oils that are required to produce a perfectly balanced food. The whole mixture was homogeneized and spray dried at a moderate temperature to avoid loss of vitamin value. The dried powder was then packed in tin cans, the air was removed and replaced by nitrogen, and the cans were sealed to prevent contamination from the outside or the development of rancidity in the product itself. Reliquefaction of this preparation, in the proportions of 35 Gm. of the powder to 8 ounces (236 cc.) of boiled water, gave the following formula:

	Per Cent
Protein	3.6
Fat	3.07
Carbohydrate	7.3
(5.2 per cent added, with 6 per cent assimilable sugars)	

Formula of the Powder

	Percentage	
Moisture	2.50	
Protein	23.69	
Fat	20.20	
Carbohydrate	48.31	
Total ash	5.30	
Starch	0.50	
p_H	5.5	(reliquefied)

One ounce of this powder equals 125 calories. One ounce of the reliquefied preparation equals approximately 19.4 calories.

CLINICAL STUDY

The infants selected for feedings of soy bean milk were those physically conforming to the "normal" or "average" and were taken from three sources: dispensary practice, private practice and an infant asylum. They were studied in two groups: (1) breast-fed babies receiving an insufficient quantity from the mothers, and (2) babies fed exclusively on soy bean milk. In the first group, each nursing period was complemented by varying quantities of the soy bean milk. The average age when the soy bean milk was started was about 4 weeks. The group of infants observed at St. Ann's were given additional feedings of a cereal-vegetable pulp consisting of 25 per cent of vegetable (spinach, beets, etc.) and 75 per cent of cereal (one-half Farina and one-half Ralston) at the age of 3 months. The remaining babies were given food supplements at about six months, consisting of cereals, vegetables and soups. The soy bean milk, with few exceptions, was well taken. Occasionally an infant rebelled at the flat taste. The food was well tolerated in almost every case. In a few instances, the babies vomited and showed signs of intolerance.

Preparation of the "Milk."—The powder was used in the proportion of 35 Gm. to 8 ounces of boiled water. In the majority of cases the mixture was not boiled. This "milk" has a grayish-white appearance, is in fine suspension, and has about the same "body" to it as cow's milk. The taste is flat, and there is a slight soya odor. The suspension passes through the ordinary nipple holes without difficulty.

Progress in Weight and Development.—The composite charts (1 and 3) illustrate the gains in both groups over a period of twenty-four weeks. (The heavy black line represents the Holt "normal" or "average" curve.) In the group fed on soy bean milk alone (chart 3), it will be seen that the curves, for the most part, parallel the Holt line. The weekly gains, as with animal milks, were variable, but a good average gain was maintained in a large proportion of cases. In some instances the gains were slow (from 3 to 5 ounces [85 to 141.7 Gm.]

per week), but the general health and condition of these babies was good, and their resistance to infection was on a par with milk-fed babies. Unusually good gains were made by some infants (from 10 to 12 ounces [283.5 to 340.2 Gm.] in a week). Charts 5, 6 and 7 show in detail the progress made by three babies in this group.

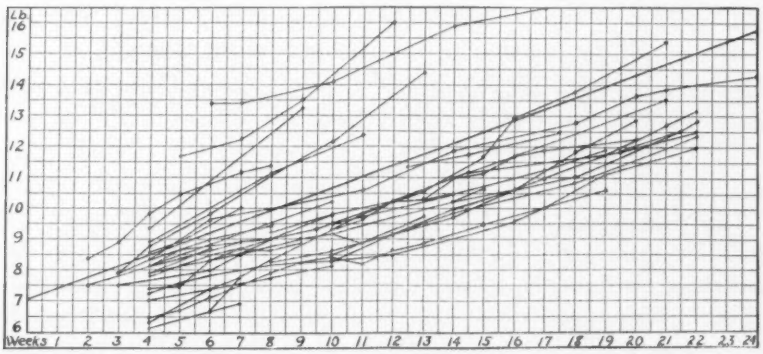

Chart 1.—Curves of the growth of infants fed breast and soy bean milk.

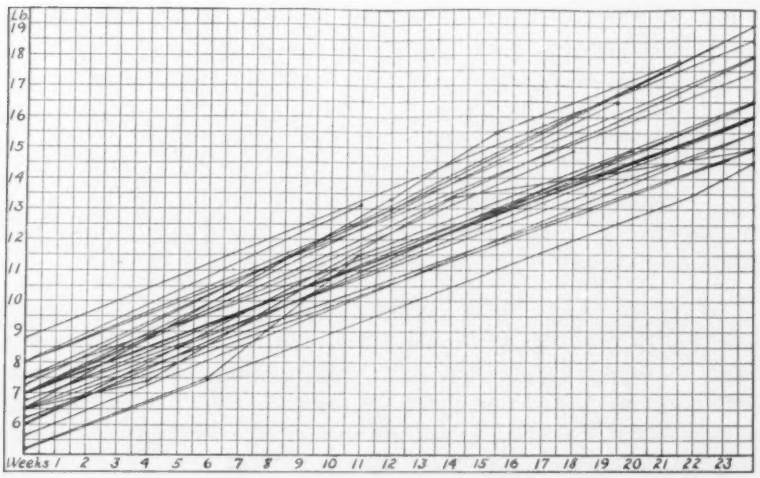

Chart 2.—Curves of the growth of infants fed a breast and cow's milk preparation (mixed).

In the second group (chart 1) the weight curves, for the majority, fall below the Holt line; however, they parallel the line with fair consistency, showing steady gains.

Chart 2 was prepared from the curves of twenty-five cases from private practice, selected at random, in which the complemental feedings

consisted of whole milk formulas, SMA, Similac, protein milk, etc. In comparing these with the curves of the babies fed on soy bean milk, one must make some allowance for the existing conditions of environment, care and hygiene. The subjects chosen from private practice were reared and fed under excellent conditions of environment, had exceptional care and developed under optimal hygienic conditions. The dispensary group

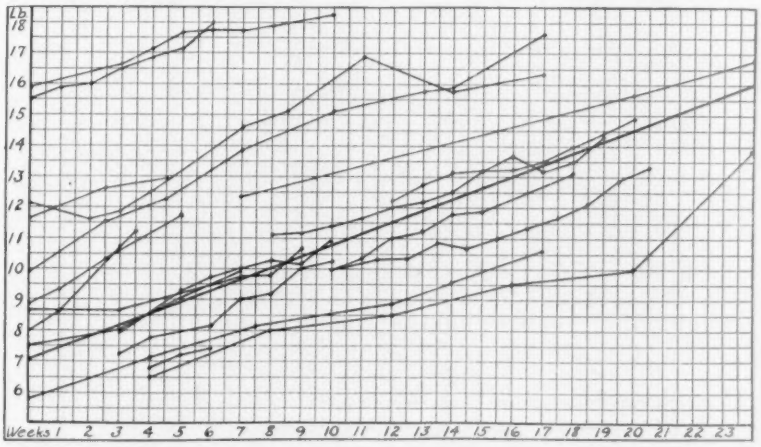

Chart 3.—Curves of the growth of infants fed soy bean milk.

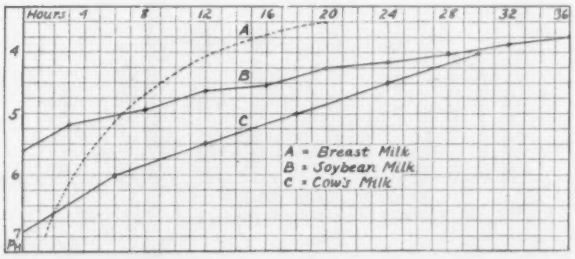

Chart 4.—Titration curves for soy bean and mother's milk. The milk was prepared as the mother would prepare it in the home. A different sample of 50 cc. volume was taken for the determination of each point on the curve. The sample was allowed to stand for two hours, to come to equilibrium, and then the acidity was determined with the quinhydrone electrode. This is the most accurate technic so far developed for determining the acidity of food.

of infants did not enjoy these conditions; their environment and hygienic care were not conducive to rapid gains in weight.

All our babies were given daily doses of cod liver oil (4 cc.) and adequate amounts of orange juice. Tissue turgor was good in nearly

all cases, and the general development was parallel with that of infants fed on milk from animals. There were occasional gastro-intestinal upsets, but these cases were invariably associated with parenteral infections, and progressed favorably with the elimination of infections and other health-retarding factors.

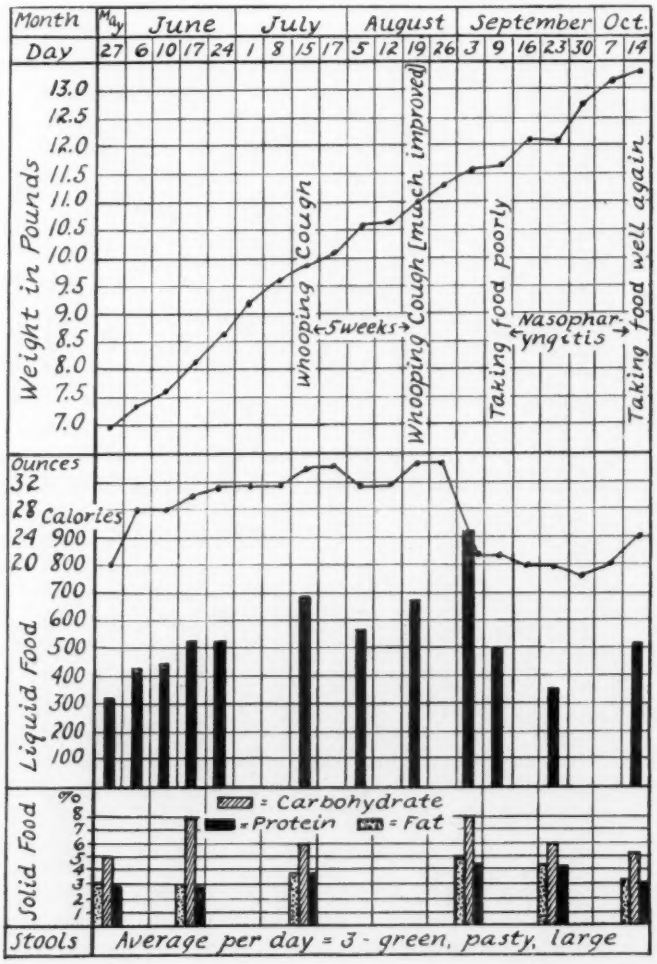

Chart 5.—Baby D began to take soy bean milk at the age of 3 weeks. The chart shows the caloric intake, the gains in weight and the intake of food.

THE STOOLS

The stools, grossly, were large, dark green, soft and well digested. The average number was three or four daily, but there were cases in which as many as six and seven were passed. It is interesting to note that in the cases in which the stools were frequent the gains were not

good. This suggested to us some defect in the metabolic processes due, possibly, to a poor assimilation of protein and an abnormal nitrogen balance.

Samples of the stools of three different infants were submitted to Dr. Ecker (Western Reserve School of Medicine) for examination, with particular reference to the flora. His report follows.

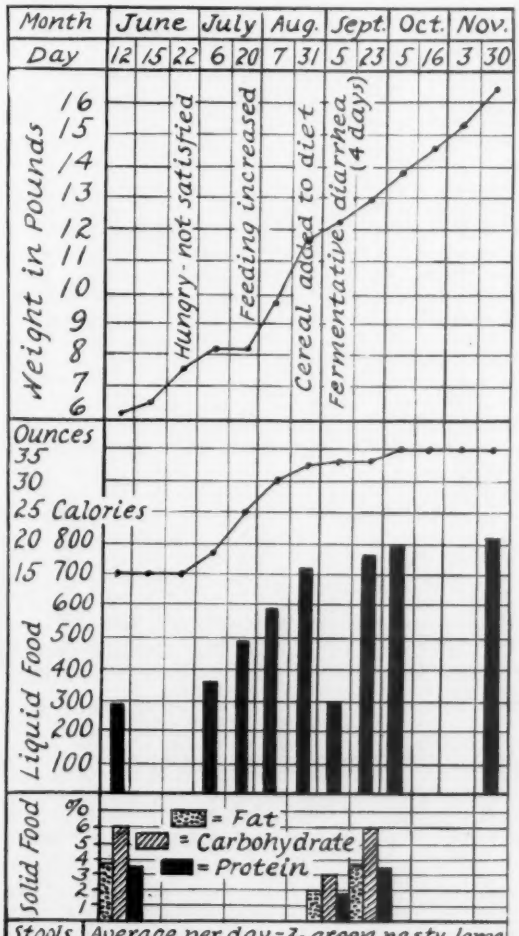

Chart 6.—Baby P began to take soy bean milk at the age of 1 month. The chart shows the caloric intake, the gains in weight and the intake of food.

Physical and Chemical Characteristics.—The stools were of normal consistency and greenish. No foul odor was noted. They were slightly acid to litmus, bromthymol blue, and alizarin. They were boiled for half an hour and tested for starch by the usual iodine method. No starch was

found. Ether extractions were then made to determine the presence of free fat, but none was noted when the ether was evaporated on paper.

Bacteriologic Findings.—Small pieces (the size of a pea) of the stools were emulsified in 2 cc. of sterile physiologic solution of sodium chloride and vigorously shaken by means of Wright's eccentric hand centrifuge. The suspensions were plated on litmus-agar broth, and at the same time cultures were made in tall column brain broth mediums

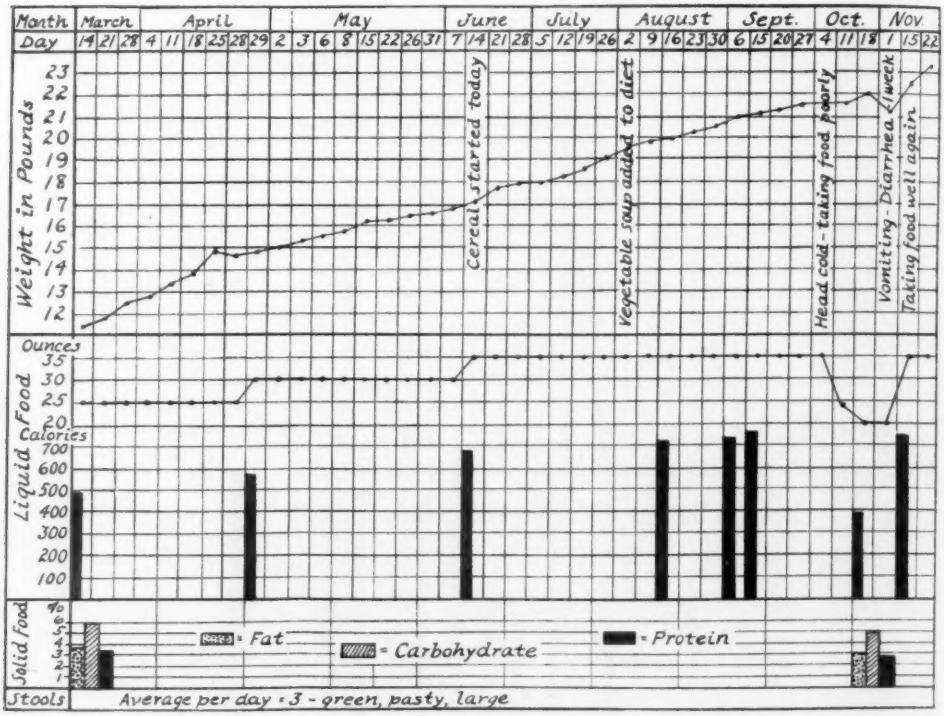

Chart 7.—Baby W began to take soy bean milk at the age of 6 weeks. The chart shows the caloric intake, the gains in weight and the intake of food.

and sealed with petrolatum. The same suspensions were also smeared on slides and stained by Gram's (Jenson's) method. All incubations were made at 37 C.

The litmus-agar-lactose plates yielded the usual Bacillus coli and B. lactis-aerogenes colonies and small white colonies of ovoid cocci (enterococci). The stool of Baby G showed many of the latter colonies. A few chromogenic organisms were also isolated. The brain broth mediums yielded gram-negative diplococci and a rod of variable size, the

variable organism being a B. coli. The Gram smears gave the following results:

Percentage of gram-negative organisms to total gram-positive organisms:

Stool 1	6
Stool 2	11
Stool 3	16

Percentage of gram-positive cocci (diplococci or short chains) to gram-positive rods:

Stool 1	26
Stool 2	17
Stool 3	14

Stool 3 showed 0.8 per cent of spore-bearing organisms. One organism with a terminal spore was noted, while the others contained central spores.

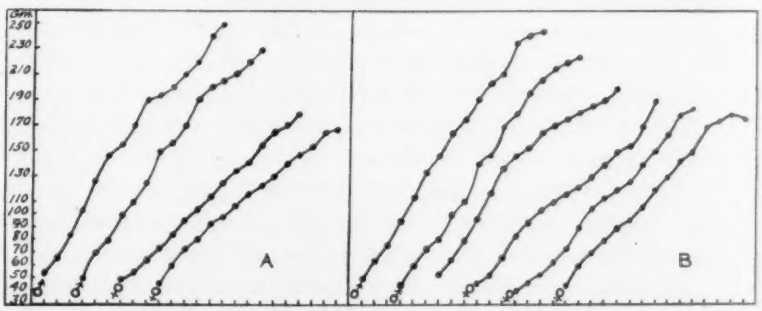

Chart 8.—Curves showing the growth of rats on a soy bean-supplement diet (*A*) and on a soy bean milk diet only (*B*). Comparative gains are shown. The diet in *A* consisted in: soy bean milk plus a daily supplement of 500 mg. of Harris medicinal yeast and 50 mg. of Harris cod liver oil.

Percentage of gram-positive thick rods (B. subtilis and B. aerogenes) to slender, slightly curved gram-positive rods (B. bifidus-acidophilus):

Stool 1	20
Stool 2	9
Stool 3	14

Stool 1 yielded 0.4 per cent of gram-positive spindle-shaped organisms. The three stools, therefore, showed a strongly gram-positive character with a predominance of gram-positive rods as usually seen in the stool of the normal breast-fed infant.

COMMENT

While the majority of the infants in this preliminary study did well on vegetable (soy bean) milk feeding, a certain group failed to show

satisfactory gains. By this we mean that their average weekly gains ranged from 3 to 4 ounces, with occasional stationary periods. In these cases there were no apparent infections, and, with the exclusion of these factors, we considered them in the light of metabolic deficiencies.

An interesting point was noted in regard to the boiling of the preparation. In those instances in which the mothers were instructed to boil the soy bean mixture from three to five minutes, we found that the stools were less frequent and at times less bulky. Apparently some change takes place, probably in the proteins, in the process of boiling There is reason to believe that the availability of the protein is increased.

In attempting to fathom the cause or causes of these slow gains in some infants, we considered the protein as the underlying factor. The percentage of protein approaches that of cow's milk and is greater than that of breast milk. The availability of this vegetable protein, however, becomes the issue of importance from the nutritional standpoint. Does this protein give a high coefficient of digestibility and utilization, or does a large part of it represent a metabolic loss with a negative nitrogen balance? Elsewhere [11] in this paper we have called attention to Tso's statement concerning the value of the protein in relation to the caloric intake. Tso and Fu-T'Ang Chu [15] investigated the nitrogen metabolism in two male infants (4 and 7 months old) who were given formulas of soy bean milk furnishing approximately 18.5, 13.5, 10.5 and 8.5 per cent of protein calories, respectively, but the same number of total calories per kilogram of body weight. In one period the protein of cow's milk was fed at a 12.2 per cent level of caloric intake. They found that at each of the graded levels of the intake of protein the nitrogen balance was positive, and that the higher the intake of protein the greater was the retention. Retention was better on a caloric intake of 12.2 per cent in cow's milk proteins than on an intake of 18.5 per cent of soy bean milk protein. The absorption of soy bean nitrogen was distinctly lower than that of cow's milk nitrogen.

Investigations on the nitrogen metabolism in some of our infants fed soy bean milk are being conducted and, along with other studies, will be reported later.

A characteristic feature of the stools resulting from the feeding of soy bean milk is the large bulk. The residue is at least twice that of human or cow's milk. We are unable to state definitely, at the present time, just what factors enter into the production of the large fecal residues. We are inclined to believe, however, that the cellulose "rough-

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15. Tso, E., and Fu-T'Ang Chu: The Nitrogen Metabolism of Infants on Graded Intake of Soybean "Milk" Proteins, Proc. Soc. Exper. Biol. & Med. **28:** 218, 1930.

age" of the soy bean plays some part. McCance and Lawrence [16] stated that cellulose and cell membranes are popularly supposed to add bulk to the feces by virtue of their indigestibility, and thus to counteract constipation by stimulating the wall of the intestine to contract. In one experiment Rubner [17] found that a man who ate 519 Gm. of the finest wheat flour in the form of bread excreted feces daily weighing about 120 Gm. (wet weight). The addition of 50 Gm. of cell membranes in the form of powdered straw led to an excretion of feces weighing nearly 300 Gm., but only 37 Gm. of these were cell membranes. The rest was made up of detritus and products of glandular activity, including water, and it is to this mixture that the increased bulk of feces is believed to be due. It is known that fruits and vegetables give a large increase of detritus in the feces, yet their cell membranes are relatively well digested and contribute little bulk to the feces. It has been suggested, therefore, that it is chiefly by virtue of the gland stimulation that the cell membranes exert a laxative action.

Jones and Waterman [18] have called attention to the presence of a toxic principle, gossypol, in cotton seed kernels. The thought has been projected that this might act as a stimulant to glandular activity. However, we find that rough laboratory tests of the raw and cooked soy beans have not shown the presence of either gossypol or its break-down product, d-gossypol. We suggest, however, that some irritating chemical substance is present in the bean, which causes a loss, possibly of glandular material, from the subject fed soy bean materials. Since boiling has been shown to reduce this loss, it is thought that this harmful material either combines with some other substances in the mixture to form a nontoxic material, or that it is actually destroyed or converted into a harmless form.

In this connection we might add that the cotton seed oil used in our preparation is a pure product and free from the toxic principles mentioned. That the active substances causing the large fecal residues is present in the soy bean flour has been demonstrated in an investigation conducted by us. One of our babies was fed soy bean flour minus the additions that were included in our synthetic soy bean food. We found that the stools were much larger than those from infants fed the soy bean mixture.

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16. McCance, R. A., and Lawrence, R. D.: The Carbohydrate Content of Foods, Medical Research Council, Special Report Series, no. 135, London, His Majesty's Stationery Office, 1929.

17. Rubner: Arch. f. Anat. (special no.), 1915, p. 74.

18. Jones, D. B., and Waterman, H. C.: J. Biol. Chem. **56**:501, 1923.

SUMMARY

1. A preliminary study of the feeding of soy bean (vegetable) milk has been made on fifty infants over a period of a year.

2. The progress in weight and the state of nutrition shown have demonstrated that the soy bean, with the addition of sugars and various mineral salts, can be made an adequate food for infants.

3. The preparation used has been shown to contain adequate amounts of the essential vitamins.

4. The stool flora resembles that of the normal, breast-fed baby.

5. The economic features (mass production and low cost) are especially significant in a consideration of soy bean milk as an infant food.

6. It compares favorably with the milk of animals from the standpoint of nutritional availability and biologic value.

An additional hundred babies are at present under observation on a diet of soy bean milk, either as a complement to breast milk or as an exclusive food. These studies will be reported at a later date.

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SERUM PROTEINS IN INFANCY AND IN CHILDHOOD

EFFECTS OF MALNUTRITION AND OF ACUTE AND CHRONIC INFECTIONS ON SERUM PROTEINS IN INFANCY AND IN CHILDHOOD

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New theories have been advanced in recent years relating to the effect of malnutrition on the serum proteins. During and after the World War, when underfeeding of large portions of the European population was widespread, there resulted a definite clinical condition, the so-called "war edema" or "Oedemkrankheit," characterized by varying degrees of edema, physical and mental debility and rapid amelioration of symptoms when an adequate diet was supplied. The condition was definitely related by observers, such as Budzynski and Chelchowski,[1] Park[2] and Jansen[3] to dietary deficiency, especially in proteins.

On the basis of Kohman's[4] experimental work with the feeding of protein-deficient diets to rats, amplified by Frisch, Mendel and Peters,[5] in which edema and low serum proteins resulted, Peters and his co-workers[6] have postulated the direct effect of malnutrition on the serum proteins and a lowering especially of the serum albumin. They observed edema on thirty-six occasions in malnourished patients, finding low serum proteins in every case but one.

From the Department of Pediatrics of the University of Chicago. This material is from a thesis presented for the degree of Master of Science, University of Chicago, June, 1931.

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2. Park, F. S.: War Edema, J. A. M. A. **70**:1826 (June 15) 1918.

3. Jansen, W. H.: Die Oedemkrankheit, Deutsches Arch. f. klin. Med. **131**: 144, 1919.

4. Kohman, E. A.: Experimental Production of Edema as Related to Protein Deficiency, Am. J. Physiol. **51**:378, 1920.

5. Frisch, R. A.; Mendel, L. B., and Peters, J. P.: The Production of Edema and Serum Protein Deficiency in White Rats by Low Protein Diets, J. Biol. Chem. **84**:167, 1929.

6. Bruckman, F. S.; D'Esopo, L. M., and Peters, J. P.: The Plasma Proteins in Relation to Blood Hydration. IV. Malnutrition and the Serum Proteins, J. Clin. Investigation **8**:577, 1930. Bruckman, F. S., and Peters, J. P.: The Plasma Proteins in Relation to Blood Hydration. V. Serum Proteins and Malnutritional or Cachectic Edema, J. Clin. Investigation **8**:591, 1930.

Underweight and malnutrition resulting from deficient diet and from disease are of relatively frequent occurrence in the early years of life. It was therefore deemed of interest to study the effects on the serum proteins of infants and children of malnutrition due to dietary deficiency, as contrasted with malnutrition due to acute and chronic infections.

The patients used for the study were from the outpatient department and wards of the Bobs Roberts Hospital, the Nancy Adele McElwee Memorial Orthopedic Hospital, the Clinic of the Home for Destitute Crippled Children and the Country Home for Convalescent Children, all connected with the clinics of the University of Chicago.

TABLE 1.—*Serum Proteins in Normal Infants and Children*

	Sex	Age	Albumin	Globulin	Total Proteins	A/G
J. W.	M	4 wks.	4.08	1.62	5.70	2.51
B. K.	F	3 wks.	4.20	1.77	5.97	2.37
B. E.	M	3 mos.	4.92	1.98	6.90	2.48
B. B.	M	3 mos.	4.66	1.60	6.26	2.90
B. M.	M	5 mos.	4.42	1.51	5.93	2.92
B. F.	M	6 mos.	4.18	1.28	5.46	3.26
Average.....			4.41	1.63	6.04	2.74
E. F.	F	2 yrs.	6.64	1.67	8.31	3.97
G. R.	F	8 yrs.	5.14	2.28	7.42	2.25
L. T.	M	8 yrs.	5.00	2.18	7.18	2.29
H. P.	F	8 yrs.	4.88	2.39	7.27	2.04
C. J.	M	9 yrs.	4.42	2.35	6.77	1.88
J. C.	M	11 yrs.	4.88	2.25	7.13	2.17
J. C.	M	11 yrs., 3 mos.	4.98	2.30	7.28	2.16
I. T.	F	14 yrs.	4.67	2.35	7.02	1.98
A. V.	F	14 yrs.	4.84	2.40	7.24	2.01
Average.....			5.06	2.23	7.29	2.32

The blood specimens were usually collected in the morning after a twelve hour fast. Since Rowe [7] and others have shown that changes in the content of plasma protein after meals are rather small, the blood in some cases (clinic material, Convalescent Home) was collected during the day. For the infants, longitudinal sinus or external jugular punctures were made; for the older children, the blood was taken from the cubital vein, minimal stasis being used. The samples of blood were placed on ice for several hours to allow retraction of the clot. In accordance with the suggestion of Greenberg,[8] no serum was allowed to remain longer than over night before the determinations were made.

For the determinations, the colorimetric method of Greenberg [8] was used. This method was chosen because of its demonstrated accuracy, ease and comparative rapidity of determinations and because it is pos-

7. Rowe, A. H.: The Effect of Muscular Work, Diet and Hemolysis on the Serum Proteins, Arch. Int. Med. **19**:499 (April) 1917.

8. Greenberg, D. M.: The Colorimetric Determination of the Serum Proteins, J. Biol. Chem. **82**:545, 1929.

sible to carry out determinations on small amounts of serum, a decided advantage when working with infants.

The figures for normal infants and for children (table 1) are in agreement with those secured by other authors, as Achard [9] and Duzar and Rusznyak [10] for infants and Greenberg,[8] Rowe,[11] Kahn [12] and Fahr and Swanson [13] for older children and adults. Higher figures have been secured by those investigators who used refractometric methods. The points of interest in our observations for normal children are (*a*) low total proteins in infants, as compared with older children and adults, and (*b*) low globulin and correspondingly high albumin-globulin ratio in infants.

The children included in the study of malnutrition (table 2) were underweight, as evidenced by the index of nutrition calculated from the

TABLE 2.—*Serum Proteins in Children Who Were Underweight and Malnourished*

	Sex	Age	Index of Nutrition	Albumin	Globulin	Total Proteins	A/G
R. V.	M	2½ mos.	—40%	4.32	1.38	5.70	3.13
G. I.	M	14 mos.	—23%	5.05	2.00	7.05	2.52
G. I.	M	20 mos.	—13%	5.71	2.48	8.19	2.29
M. K.	F	2 yrs.	—28%	4.62	2.08	6.70	2.22
J. O.	F	7 yrs.	—16%	5.47	1.54	7.01	3.55
L. V.	F	8 yrs.	—20%	5.00	2.95	7.95	1.69
R. W.	M	8 yrs.	—15%	6.20	2.03	8.23	3.05
G. Y.	M	9 yrs.	—34%	4.74	2.03	6.77	2.33
W. C.	M	9 yrs.	—22%	4.80	2.06	6.86	2.33
M. H.	F	14 yrs.	—28%	4.43	2.04	6.47	2.17
Average (older children)*.....				5.04	2.09	7.13	2.43

* The second determination on G. I. is not included.

tables of Baldwin and Wood, and had histories of deficient diet or some noninfectious condition interfering with normal assimilation of food. It appears that ordinary degrees of malnutrition and underweight, when the factor of infection is excluded, are not attended by any significant alteration in the serum proteins.

9. Achard, C.; Bariety, M., and Codounis, A.: L'équilibre protéique du serum comparé dans le sang de la mère et le sang du cordon ombilicale, Compt. rend. Soc. de biol. **102**:984, 1929.

10. Duzar, J., and Rusznyak, S.: Examination of Plasma Protein in Infants, Am. J. Dis. Child. **28**:441 (Oct.) 1924.

11. Rowe, A. H.: The Albumin and Globulin Content of Human Blood Serum, Arch. Int. Med. **18**:455 (Oct.) 1916.

12. Kahn, M.: The Protein and Lipin Content of Blood Serum in the Nephritides, Arch. Int. Med. **25**:112 (Jan.) 1920.

13. Fahr, G., and Swanson, W. W.: The Quantities of Serum Albumin, Globulin and Fibrinogen in the Blood Plasma in Acute and Chronic Nephropathies, Arch. Int. Med. **38**:510 (Oct.) 1926.

ALTERATIONS IN SERUM PROTEIN DURING INFECTIONS

Acute Infections.—Alterations in the serum proteins as a result of acute infections have been reported by a large number of authors. The usual observations are (*a*) minimal lowering of total protein, (*b*) normal or increased globulin and (*c*) considerably decreased albumin. Mensi [14] reported low total proteins in all acute infectious diseases of childhood, while Starlinger,[15] Wiener and Wiener [16] and Schock [17] found an altered albumin-globulin ratio. An unusually marked increase in globulin was noted by Epstein [18] in pneumonia; in lobar pneumonia

TABLE 3.—*Serum Proteins in Children with Acute Infections*

	Age	Condition	Albumin	Globulin	Total Proteins	A/G
A. P.	1½ yrs.	Bronchopneumonia, 4th day; temp. 41 C.....	3.98	1.64	5.62	2.43
S. T.	2½ yrs.	Bronchopneumonia, sepsis; temp. 40 C.; died	4.78	2.20	6.98	2.17
E. E.	7 yrs.	Lobar pneumonia, 7th day; temp. 38.8 C....	5.06	2.58	7.64	1.96
E. E.	7 yrs.	Temp. normal for 1 week.....	5.48	2.94	8.42	1.86
D. W.	6 yrs.	Lobar pneumonia, 4th day; temp. 40 C.....	3.76	2.80	6.56	1.34
D. W.	6 yrs.	9 days later, empyema.....	4.02	3.57	7.59	1.12
D. W.	6 yrs.	5 weeks later, improved.....	4.93	3.84	8.77	1.28
M. O.	3 wks.	Acute nephritis, edema.....	3.37	1.82	5.19	1.85
R. R.	4 yrs.	Acute nephritis	4.83	2.64	7.47	1.83
J. M.	12 yrs.	Acute nephritis	4.09	2.22	6.31	1.84
J. M.	12 yrs.	2 months later, chronic nephritis.....	4.21	2.05	6.26	2.05
J. D.	5 mos.	Diarrhea, acute pharyngitis, 3d day.....	3.82	2.04	5.86	1.87
J. D.	5 mos.	Normal for 10 days.....	4.43	2.69	7.12	1.64
E. F.	9 mos.	Diarrhea and pharyngitis, 2d day.....	4.46	1.45	5.91	3.07
E. F.	9 mos.	Normal for 2 days.....	5.26	1.80	7.06	2.92
R. R.	4 yrs.	Dysentery, Flexner, 3 weeks' duration.....	4.74	1.84	6.58	2.57
D. L.	9 yrs.	Paratyphoid fever, 1 week's duration.....	3.96	2.19	6.15	1.80
R. W.	8 yrs.	Acute sinusitis	4.15	2.12	6.27	1.95
S. Z.	9 yrs.	Acute pharyngitis	5.15	2.22	7.37	2.32
J. C.	10 yrs.	Acute appendicitis	4.98	1.68	6.66	2.96
B. S.	10 yrs.	Acute rheumatic fever.....	5.59	2.67	8.26	2.09
B. S.	10 yrs.	Normal for 6 days.....	5.22	2.22	7.44	2.35
R. L.	14 yrs.	Infected cyst	5.00	1.78	6.78	2.80

Loeper [19] stated that the globulin content sometimes doubles immediately after the crisis.

The common impression that the blood serum is concentrated with high serum proteins in diarrheal diseases is apparently true only when

14. Mensi, E.: The Albumin Content of the Blood Serum in Children, Pediatria **29**:577, 1921; abstr., J. A. M. A. **77**:895 (Sept. 10) 1921.

15. Starlinger, W.: Ueber das Verhalten der zirkulierenden Eiweisskörper des menschlichen Plasma unter normalen und krankhaften Bedingungen, Deutsche med. Wchnschr. **54**:731, 1928.

16. Wiener, H. J., and Wiener, R. E.: Plasma Proteins, Arch. Int. Med. **46**: 236 (Aug.) 1930.

17. Schock, A.: Ueber Eiweiss-schwankungen in Blutserum bei akuten Infectionskrankheiten, Schweiz. med. Wchnschr. **56**:1017, 1926.

18. Epstein, A. A.: A Contribution to the Study of the Chemistry of Blood Serum, J. Exper. Med. **16**:719, 1912.

19. Loeper, M.; Ravier, J. de Sèze, and Lebert, M.: La globulinémie à la période critique de la pneumonie, Compt. rend. Soc. de biol. **101**:423, 1929.

the dehydration is marked and acute. In 1909 Reiss [20] noted that the total proteins were low in some cases of acute gastro-enteritis, while Marriott [21] has shown that if the dehydration is long continued the plasma solids and proteins are lowered; this he attributed to a breakdown in the proteins of the body, with liberation of bound water. McIntosh, Kajdi and Meeker [22] found a variable content of plasma proteins during dehydration from diarrhea.

In the patients with pneumonia and acute nephritis (table 3), slight decreases in the total proteins and albumin and a lowered albumin-globulin ratio are seen. The globulin shows little change. In the cases of diarrhea there are slightly low total proteins during the attack, not

TABLE 4.—*Serum Proteins in Children with Chronic Infections*

	Age	Condition	Albumin	Globulin	Total Proteins	A/G
A. K.	8 yrs.	Syphilis of bone, Wassermann 4 plus	4.94	2.09	7.03	2.36
D. W.	13 yrs.	Syphilis of central nervous system, treated for 2 years	5.03	2.37	7.40	2.12
K. N.	13 yrs.	Asymptomatic syphilis, untreated; Wassermann 4 plus	4.78	2.28	7.06	2.09
R. S.	2 yrs.	Childhood tuberculosis	4.64	2.20	6.84	2.11
G. P.	2 yrs.	Childhood tuberculosis	4.58	1.83	6.41	2.50
G. P.	2 yrs.	Two months later	5.38	2.35	7.73	2.28
N. K.	2 yrs.	Diabetes mellitus	4.92	1.76	6.68	2.80
R. H.	6 yrs.	Diabetes mellitus	4.98	1.96	6.94	2.54
L. H.	10 yrs.	Diabetes mellitus	5.52	1.85	7.37	3.00
J. N.	11 yrs.	Diabetes mellitus	5.12	2.93	8.05	1.75
R. S.	12 yrs.	Asthma	6.43	2.30	8.73	2.79
D. H.	12 yrs.	Hodgkin's disease	4.15	2.90	7.05	1.43
R. Z.	9 yrs.	Bronchiectasis	4.57	2.97	7.54	1.53
A. K.	14 yrs.	Otitis media, chronic	5.04	2.46	7.50	2.05
Average			4.97	2.30	7.27	2.23

confined to either protein fraction. The other acute infections show no regularity of change. In all of the cases followed, improvement in the patient's condition was accompanied by a rise in the total proteins to a normal level.

Chronic Infections.—An almost universal tendency to increased globulin and decreased albumin fractions seems to be the rule for chronic infections. The total serum proteins may be unchanged or vary slightly. Starlinger,[15] who investigated the proteins in the course of many infections, reported a lowered albumin-globulin ratio in most of the chronic infections, including bronchiectasis, asthma, tuberculosis,

20. Reiss, E.: Untersuchungen der Blutkonzentration des Säuglings, Jahrb. f. Kinderh. **70**:311, 1909.

21. Marriott, W. M.: Anhydremia, Physiol. Rev. **3**:275, 1923.

22. McIntosh, R.; Kajdi, L., and Meeker, D.: Blood Volume and Plasma Electrolyte Changes in the Dehydration of Infants, J. Clin. Investigation **9**:333, 1930.

syphilis, malaria, chronic nephritis and nephrosis. Schiff and Roser [23] likewise found hyperglobulinemia during chronic infections of children.

Attention during the present investigation has been centered on tuberculosis of the bones and joints and chronic osteomyelitis as typical examples of chronic infections of childhood which offer opportunity to study changes over long periods of time with a fairly large amount of available material. Several other conditions (table 4) have, however, been included.

TABLE 5.—*Serum Proteins in Children with Bone and Joint Tuberculosis*

	Age	Involvement and Duration	Albumin	Globulin	Total Proteins	A/G
Bone and Joint Tuberculosis, Without Renal Involvement						
J. G.	4 yrs.	Tuberculosis of hip, 16 months	4.95	1.93	6.88	2.56
W. M.	7 yrs.	Tuberculosis of hip 2½ years	5.32	2.60	7.92	2.05
E. K.	5 yrs.	Tuberculosis of hip and foot 3 years; 4/6/31	5.00	2.10	7.10	2.38
E. K.	5 yrs.	Unchanged 5/9/31	5.23	2.00	7.23	2.61
A. K.	8 yrs.	Tuberculosis of spine 3½ years	5.16	2.21	7.37	2.33
J. B.	10 yrs.	Tuberculosis of hip 4 years	5.45	2.40	7.85	2.27
E. S.	7 yrs.	Tuberculosis of spine 4½ years	4.65	2.26	6.91	2.05
A. D.	11 yrs.	Tuberculosis of spine 5½ years	4.83	2.24	7.07	2.15
J. K.	15 yrs.	Tuberculosis of hip 6 years	5.08	2.77	7.85	1.83
J. S.	10 yrs.	Tuberculosis of hip and spine 7 years	5.13	2.19	7.32	2.34
J. P.	12 yrs.	Tuberculosis of hip 10 years	5.27	2.43	7.70	2.17
R. S.	15 yrs.	Tuberculosis of spine 12 years	5.18	2.40	7.58	2.15
R. B.	12 yrs.	Tuberculosis of spine; lung lesion	4.76	3.25	8.01	1.46
R. B.	12 yrs.	Lung improved after 5 weeks	5.18	3.31	8.49	1.56
Average, first determinations			5.06	2.40	7.46	2.14
Bone and Joint Tuberculosis, with Renal Involvement						
F. E.	16 yrs.	Tuberculosis of spine 12 years, anemia, chronic nephritis	4.42	2.48	6.90	1.78
W. P.	8 yrs.	Tuberculosis of spine 4 years, nephrosis and anasarca	2.85	1.85	4.70	1.54
W. P.	8 yrs.	Improved 1 month later	2.60	2.47	5.07	1.05
W. P.	8 yrs.	Greatly improved 2 months later	3.09	2.89	5.98	1.06
J. K.	14 yrs.	Tuberculosis of spine 9 years with nephrosis	2.82	2.22	5.04	1.27
J. K.	14 yrs.	Unchanged 1 month later	2.77	2.30	5.07	1.20

Very little deviation from the normal is seen in the ordinary chronic infections listed in table 4, with the exception of the slightly high globulin content in the cases of Hodgkin's disease and of bronchiectasis. Normal results are secured in diabetes mellitus, in childhood tuberculosis and in congenital syphilis, the finding in the last condition agreeing with the statement of Rowe [11] that no parallelism exists between the height of globulin and the Wassermann reaction.

The cases of tuberculous bone and joint disease that were studied (table 5), as well as those of chronic osteomyelitis to be presented later, were seen in the various orthopedic institutions previously mentioned. Practically all of the patients were confined to bed, with active

23. Schiff, E., and Roser, E.: Ueber das quantitative Verhalten des Albumine und Globuline im Blutserum des Säuglings, Monatschr. f. Kinderh. **19**:15, 1920.

involvement in many instances; some patients had draining sinuses, and several had secondary anemia. High caloric and high iron diets were the rule, with high protein only as indicated.

Table 5 shows normal average figures for the group without renal involvement and for the individual patients, with the exception of the last patient, R. B., who showed a high globulin content on two occasions, with a reduced albumin-globulin ratio. It is an interesting observation that these children, who had undergone a severe chronic disease over periods varying from sixteen months to twelve years and who were poorly nour-

TABLE 6.—*Serum Proteins in Children with Chronic Osteomyelitis*

	Age	Involvement and Duration	Albumin	Globulin	Total Proteins	A/G
Chronic Osteomyelitis, Without Renal Involvement						
A. W.	13 yrs.	Multiple, 13 months; temp. 38.2 C., 10/9/30...	3.83	3.14	6.97	1.22
A. W.	13 yrs.	Improved, 11/13/30	4.85	2.93	7.78	1.65
A. W.	13 yrs.	Improved, 4/10/31	4.76	2.74	7.50	1.73
A. W.	13 yrs.	Greatly improved 5/9/31.....	4.55	2.82	7.37	1.61
D. D.	12 yrs.	Tibia, 2 years.....	5.10	3.05	8.15	1.67
P. P.	13 yrs.	Femur, 3 years.....	4.56	2.99	7.55	1.52
M. P.	14 yrs.	Multiple, 5 years, marked anemia.....	5.56	3.58	9.14	1.55
B. M.	13 yrs.	Multiple, 9 years, anemia, 10/29/30.....	4.03	2.75	6.78	1.46
B. M.	13 yrs.	Improved after transfusion, 1/21/31.....	4.53	3.14	7.67	1.44
Average, first determinations.....			4.61	3.10	7.71	1.48
Chronic Osteomyelitis, with Renal Involvement						
J. V.	6 yrs.	Multiple, 2½ years, anemia, chronic nephritis, 2 to 4 plus albuminuria.....	2.95	2.43	5.38	1.21
E. G.	11 yrs.	Multiple, 2½ years, chronic nephritis, 2 plus albuminuria.....	5.09	3.12	8.21	1.63
S. J.	13 yrs.	Multiple, chronic nephritis, 1/28/31.....	4.08	2.69	6.77	1.52
S. J.	13 yrs.	Uremic symptoms for 1 month; albumin 4 plus, casts and R.B.C. 3/27/31.....	3.53	2.26	5.79	1.56
S. J.	13 yrs.	Improved, albumin 3 plus, 4/23/31.....	3.97	2.32	6.29	1.71
Average, first determinations.....			4.04	2.74	6.78	1.45

ished, as attested by evident thinness and poor tissue tone, show in every instance normal serum albumin. None of these patients received a high protein diet.

The patients who had concomitant renal involvement (table 5) exhibit a diminution in the total proteins, which is confined to the albumin fraction, the globulin remaining normal or being slightly increased. Reduction in the albumin-globulin ratio is pronounced, in the case of W. P. reaching practically 1:1. Epstein [24] was the first to show that in the type of renal involvement illustrated by the patients

24. Epstein, A. A.: Concerning the Causation of Edema in Chronic Parenchymatous Nephritis: Method for Its Alleviation, Am. J. M. Sc. **154**:638, 1917; Further Observations on the Nature and Treatment of Chronic Nephrosis, ibid. **163**:167, 1922.

W. P. and J. K. there is a distinct deficiency in blood protein; this he attributed to prolonged albuminuria for which he advocated high protein diet. His observations have been corroborated by Fahr and Swanson,[18] Schlutz, Swanson and Ziegler[25] and Moore and Van Slyke.[26] Striking improvement accompanied by increased serum proteins and diminished edema was seen in patient W. P. after a high protein diet.

Table 6 shows marked alterations in some cases of chronic osteomyelitis in the form of a universally high globulin content and a low albumin-globulin ratio. In the group without renal involvement the average globulin, 3.1 per cent, is higher than that in any other group of cases studied and is apparently significant. It seems to verify Robertson's[27] statement that streptococcic and staphylococcic infections cause greater increase in globulin than other infections. The average total protein in this group is normal, but in two of the cases with renal involvement the total protein is reduced, probably owing to the prolonged albuminuria. An increase in the level of serum protein following improvement, with no change in the diet is seen in several cases.

COMMENT

The influence of feeding and of general body nutrition on the serum proteins is a debated question. After a single meal Rowe[7] found a transitory effect, the alteration in the proteins never being greater than 0.5 per cent. Howe[28] stated that ingestion of food and fasting have little effect on the serum proteins, and Hanson[29] found no alteration in human serum proteins after starvation for from five to six days. We may therefore conclude that intake of food over a short period has only a transitory, if any, effect on the serum proteins of normal persons.

Whether this observation holds true for malnutrition over a longer period of time or for persons whose protein content has been altered by disease is more difficult to determine. Most of the work of Peters and his co-workers[6] regarding the association of low serum albumin and malnutrition was done with patients who had diseases which are known

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25. Schlutz, F. W.; Swanson, W. W., and Ziegler, M.: The Distribution of the Globulin and Albumin Fractions in the Blood and in the Urine in Nephrosis, Am. J. Dis. Child. **36**:756 (Oct.) 1928.

26. Moore, H. S., and Van Slyke, D. D.: The Relationship Between the Plasma Specific Gravity, Plasma Protein Content and Edema in Nephritis, J. Clin. Investigation **8**:337, 1930.

27. Robertson, T. B.: Principles of Biochemistry, ed. 2, Philadelphia, Lea & Febiger, 1924, p. 377.

28. Howe, P. E.: The Function of the Plasma Proteins, Physiol. Rev. **5**:439, 1925.

29. Hanson, S.: The Constancy of the Protein Quotient During Intensive Digestion and Prolonged Starvation, Immunology **3**:67, 1918.

to alter the serum proteins; therefore these men have not demonstrated that the malnutrition, as distinguished from the disease process, is the causative factor of the decreased serum albumin. In the present studies, fairly decided states of malnutrition in the absence of disease were accompanied by normal serum albumin. It is further evident that during some diseases, such as chronic osteomyelitis, there are low contents of albumin; whereas during other chronic diseases, such as tuberculosis of the bones and joints without renal involvement, there are many cases with normal albumin, although the state of nutrition is poor. It was noted, also, that in the same disease group there was little or no correlation between the state of nutrition and the height of the serum albumin.

The association of immune bodies with the globulin fraction, based on the increase in globulin observed during infections and during experimental production of antibodies, does not necessarily imply that the elevation in globulins represents an accumulation of protective substances, according to Hurwitz and Meyer.[30] They found that increase in globulin is the rule when massive infections are involved, but that mild or chronic infections and careful immunizations may produce high immunity with an unaltered globulin content of the blood. They consider the increase in globulin as only one manifestation of a disturbed metabolism.

Linder, Lundsgaard and Van Slyke [31] offered the theory that the globulin is the primitive form of blood protein to which the organism reverts in disease. Robertson [27] favored the theory that alterations in permeability are responsible for the increase in globulin. Until further studies, particularly in the field of biochemistry, have been carried out, it is impossible to fix definitely the mechanism of alterations in serum protein. The constancy of the total protein concentration, however, except in extremely advanced conditions like nephrosis, suggests an interrelation or balance between the fractions, one compensating for an increase or decrease in another.

CONCLUSIONS

1. Older children have normal values for serum protein at the same level as those in the adult. Infants have low values for total protein and particularly low values for serum globulin; this possibly has some relation to hydrolability or to absence of the infectious diseases.

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30. Hurwitz, S. H., and Meyer, K. F.: Studies on the Blood Proteins. I. The Serum Globulins in Bacterial Infection and Immunity, J. Exper. Med. **24**:515, 1916, and **25**:231, 1917.

31. Linder, G. C.; Lundsgaard, C., and Van Slyke, D. D.: The Concentration of the Plasma Proteins in Nephritis, J. Exper. Med. **39**:887, 1924.

2. No regular relationship between the state of nutrition and serum albumin content could be established.

3. Acute infections produce comparatively mild and temporary changes in the serum proteins.

4. Alterations in the concentration of serum protein during chronic infections depend on the type of infection. In the series in question the most pronounced changes were seen in (*a*) chronic osteomyelitis, which was marked by elevated values for globulin, and (*b*) renal involvement, especially nephrosis, characterized by lowered serum albumin and lowered total proteins but increase in globulins.

IMMUNIZATION AGAINST DIPHTHERIA WITH TOXOID

WITH SPECIAL REFERENCE TO THE TIME INTERVAL AND SIZE OF INJECTIONS

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It is not my purpose to discuss the relative merits of toxin-antitoxin and toxoid. This phase has been thoroughly investigated by Ramon and Helie,[1] Zingher,[2] Bloomberg and Fleming,[3] Mozer,[4] Harrison [5] and more recently in this clinic by Weinfeld and Cooperstock [6] and other observers (table 1). The conclusions arrived at by these workers are that toxoid is superior to toxin-antitoxin for the following reasons: 1. Sensitization to horse serum is eliminated. 2. The solution is more stable. 3. Fewer injections are needed. 4. The immunizing power is greater and more rapid.

The original technic as described by Ramon and Helie [1] is as follows: "An initial dose of 0.5 cc. of anatoxin is injected subcutaneously; three weeks later 1.0 cc. is injected, and in many cases if not all, a third injection of from 1.0 cc. to 1.5 cc. is given fifteen days after the second dose." They further added that two injections of anatoxin immunized from 90 to 95 per cent of patients, and three injections from 97 to 100 per cent. Immunity was acquired in from five weeks to two months.

Nesbit,[7] during the years 1928, 1929 and 1930, was able to immunize from 82 to 91 per cent of a large series of school children, using the

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1. Ramon, G., and Helie, G. I.: Diphtheria Prophylaxis in France, J. A. M. A. **91**:1028 (Oct. 6) 1928.

2. Zingher, Abraham: Immunity Results with Toxoid and Mixtures of Toxin-Antitoxin, Proc. Soc. Exper. Biol. & Med. **22**:462, 1924-1925.

3. Bloomberg and Fleming: Canad. M. A. J. **17**:801, 1927.

4. Mozer: Statistics of Four Years Anatoxin Immunization in the Naval Hospital at Berck, Presse méd. **37**:1543 (Nov. 27) 1929.

5. Harrison, W. T.: Immunizing Values of Toxoid and Toxin-Antitoxin, Pub. Health Rep. **45**:1883 (Aug. 15) 1930.

6. Weinfeld, G. F., and Cooperstock, M.: Comparative Effects of Diphtheria Toxoid and Toxin-Antitoxin as Immunizing Agents, Am. J. Dis. Child. **38**:35 (July) 1929.

7. Nesbit, O. B.: Toxoid as an Immunizing Agent, J. Indiana M. A. **23**: 479 (Oct.) 1930.

TABLE 1.—*Summary of Previous Results With Toxoid*

	Year	Number of Injections	Dosage (Cc.)			Interval Between Injections	Number of Patients Given Injections	Percentage Who Acquired Immunity	Time from the Final Injection of Toxoid Until Negative Schick Test Was Obtained
Park and Zingher: Am. J. Dis. Child. 28: 464 (Oct.) 1924	1924	3	1.0	1.0	1.0	1 to 2 wks.	1,012	86.0	3 months
	1924	2	1.0	1.0	...	1 to 2 wks.	245	68.0	3 months
	1924	3	1.0	1.0	1.0	1 to 2 wks.	401	94.0	3 months
	1924	2	1.0	1.0	...	1 to 2 wks.	83	75.0	
Zingher [2]	1925	3	0.5	0.5	1.0	2 wks.		98.0	6 weeks
	1925	2	0.5	0.5	...	2 wks.		86.4	6 weeks
	1925	1	0.5	...	...			60.0	6 weeks
Maloney and Fraser [10]	1927	2	0.5	0.5	...	1 mo.	53	70.0	6 weeks
Bloomberg and Fleming [3]	1927	2	0.5	0.5	...	1 mo.	208	68.0	13 months
	1927	2	0.5	1.0	...	1 mo.	38	84.0	8 months
Frankl, Herzog, Nobel [13]	1928	2	0.5	1.0	...	21 days	32	34.0	2 weeks
	1928	2	0.5	1.0	...	21 days	69	60.8	3 weeks
	1928	2	0.5	1.0	...	21 days	97	93.8	6 weeks
Ramon and Helie,[1] citing:									
(A) Lesne	1928						1,000	90.0	
(B) Lereboullet		2					96	94.4	4 weeks
(C) Hervier, Requin		2					200	96.4	3 months
(D) Loiseau, Lafaille		3					161	99.4	2 months
(E) Zoeller		3					47	100.0	6 weeks
(F) Hanseval, Neles		2						94.0	35 days after first injection
(G) At St. Trojan		2						100.0	6 weeks
Johan and Tomczik: Klin. Wchnschr. 9: 1868, 1930	1928–29	3	0.5	1.0	1.5	1st and 2nd=3 wks. 2nd and 3rd=2 wks.	60,000 to 70,000	70.0 to 80.0	
Nesbit [7]	1928	3	0.5	1.0	1.5	1st and 2nd=3 wks. 2nd and 3rd=2 to 3 wks.	436	82.0	"Few" weeks
	1929	3	0.5	1.0	1.5	1st and 2nd=3 wks. 2nd and 3rd=2 to 3 wks.	283	88.0	1 year
	1930	3	0.5	1.0	1.5	1st and 2nd=3 wks. 2nd and 3rd=2 to 3 wks.	597	91.0	5 to 12 months
Dick and Dick [6]	1929	3	0.5	1.0	1.5	2 wks.	100	94.0	6 weeks
Weinfeld and Cooperstock [9]	1929	2	1.0	1.0	...	21 days	89	92.0	5 to 7 months
	1929	1	1.0	...	...		15	46.0	5 to 7 months
Harrison [5]	1930	3	0.5	0.5	1.0	1 wk.	86	92.0	133 days
	1930	2	1.0	1.0	...	31 days	72	92.0	119 days
	1930	2	1.0	1.0	...	31 days	128	95.0	119 days
	1930	2	1.0	1.0	...	31 days	118	96.0	119 days
	1930	2	1.0	1.0	...	42 days	72	99.0	90 days
Cooperstock and Weinfeld [16]	1930	2	1.0	1.0	...	21 days	50	58.0	21 days
	1930	2	1.0	1.0	...	21 days	44	79.5	63 days
	1930	2	1.0	1.0	...	21 days	65	92.3	112 to 154 days
Schwartz and Janney: Am. J. Dis. Child. 39: 504 (March) 1930	1930	3	0.5	0.5	1.0	21 days	128	98.0	
Greengard [9]	1931	2	1.0	1.0	...	3 wks. and 1 wk.	100	98.0	6 weeks plus
Author's series	1931	2	1.0	1.0	...	7 days	60	87.0	14 weeks
	1931	2	1.0	1.0	...	7 days	27	85.0	16 weeks
	1931	1	1.5	...	...		13	61.0	19 weeks

dosage advised by Ramon. Dick and Dick [8] gave doses of 0.5 cc., 1 cc. and 1.5 cc. at fourteen day intervals. Schick retests made six weeks after the last injection showed that in 94 per cent of 100 patients the reaction to the Schick test was rendered negative.

As early as 1925, Zingher [2] advised that three doses of toxoid gave immunity to 98 per cent of subjects, two doses to 86.4 per cent and a single dose to 60 per cent. The interval between injections was two weeks, and the doses were 0.5, 0.5 and 1 cc.

Harrison [5] gave two doses of 1 cc. of toxoid with an interval of thirty-one days between the injections. At the end of four months immunity was produced in from 92 to 99 per cent of the children. Weinfeld and Cooperstock [6] gave two doses of 1 cc. of toxoid at an interval of twenty-one days, and obtained immunity in 92 per cent of eighty-nine adults in from five to seven months.

Greengard,[9] in a series of one hundred infants, obtained immunity in 98 per cent after six weeks. Two doses of 1 cc. of toxoid were given at intervals of three weeks and of one week. He did not state the comparative number of infants whose reaction to the Schick test was rendered negative in relation to the time interval of the injections.

Bloomberg and Fleming [3] worked with smaller doses of toxoid. Two doses of 0.5 cc. each were given at an interval of thirty-one days. Sixty-eight per cent of two hundred and eight patients were immune in thirteen months. Maloney and Fraser,[10] using the same dosage and intervals, produced immunity in 70 per cent of fifty-three patients in six weeks. Bloomberg and Fleming [3] also gave toxoid to a series of patients in which the second dose was increased to 1 cc.; that is, a first dose of 0.5 cc. was given, and in thirty-one days a second dose of 1 cc. was given. Eighty-four per cent of the thirty-eight patients gave negative reactions to the Schick test in eight months (table 1).

In all of the cases referred to, immunity was considered to be present when manifested by a negative Schick test. The time when immunity was acquired was calculated from the date of the last injection of toxoid.

In a general consideration, the variable factors have been the size of the individual doses of toxoid and the time interval of the injections. With Ramon's technic, six weeks were necessary to complete the series of injections. In Harrison's series, thirty-one days were required. Weinfeld and Cooperstock [6] required twenty-one days. In a portion of Greengard's cases [9] seven days only were required. The results in all cases were apparently satisfactory as to final immunity.

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8. Dick, G. F., and Dick, G. H.: Immunization Against Diphtheria, J. A. M. A. **92**:1901 (June 8) 1929.

9. Greengard, H.: Diphtheria Toxoid in Infancy, J. A. M. A. **97**:228 (July 25) 1931.

10. Maloney and Fraser: Am. J. Pub. Health **17**:1027, 1927.

Maloney and Fraser [10] and Bloomberg and Fleming [3] have shown that two doses of toxoid each containing 0.5 cc. or two doses of toxoid with a total volume of 1.5 cc. do not give immunization in a large enough percentage to warrant continued use. An analysis of table 1 shows that approximately 2 cc. of toxoid is necessary to produce satisfactory immunity as measured by a negative Schick test.

The problem considered in this study was the determination of what percentage of patients could be immunized if two doses of toxoid, each containing 1 cc., were given with a time interval of only seven days as compared with longer intervals. My associates and I were further interested in considering the effect of toxoid given at the period of prevalence of diphtheria when time is of the utmost importance.

TABLE 2.—*Series 1—Sixty-Five Nurses With Positive Reactions to the Schick Test Were Given Two Injections of 1 Cc. of Toxoid Seven Days Apart*

	1 Week*	2 Weeks	3 Weeks	4 Weeks	14 Weeks
Number of nurses appearing for Schick tests.....	41	41	41	41	41
Number of nurses rendered negative to Schick test..	14	19	25	30	33
Percentage rendered negative to Schick test.....	34%	46%	61%	73%	80%

* The time recorded for the Schick tests indicates the time elapsed after the second injection of toxoid.

TABLE 3.—*Series 1—Sixty-Five Nurses With Positive Reactions to the Schick Test Were Given Two Injections of 1 Cc. of Toxoid Seven Days Apart*

	1 Week*	2 Weeks	3 Weeks	4 Weeks	14 Weeks
Number of nurses appearing for Schick tests.....	61	51	59	62	60
Number of nurses rendered negative to Schick test..	26	21	37	44	52
Percentage rendered negative to Schick test.....	43%	41%	63%	71%	87%

* The time recorded for the Schick tests indicates the time elapsed after the second injection of toxoid.

The following observations were made on nurses. The work was begun in February, 1931, and completed in July, 1931. The majority of the nurses were from small towns and farms. A few were from large cities (population of 50,000 and more). A single brand of commercial toxoid was used throughout the series.

EXPERIMENTS

SERIES 1 (tables 2 and 3).—A large group of graduate nurses were given Schick tests, and sixty-five gave positive reactions. Two injections of 1 cc. each of commercial toxoid were given to these sixty-five nurses at an interval of seven days. Schick tests were made at weekly intervals for four weeks. A final Schick test was made fourteen weeks after the second injection of toxoid. The weekly Schick tests were begun seven days after the second injection of toxoid.[11]

11. Toxoid injections were almost invariably given high over the left deltoid. Schick tests were all made on the inner surface of the left forearm, with the control on the inner surface of the right forearm. At no time was a second test or control made on the exact area previously used.

Owing to the difficulties of accommodating the schedule of the nurses with the time available for the Schick tests, the number of nurses tested varied each week. Forty-one of the sixty-five, however, were tested according to the desired schedule. The results are tabulated in table 2. One week after the second injection of toxoid, fourteen, or 34 per cent, gave negative reactions; after two weeks, nineteen, or 46 per cent; after three weeks, twenty-five, or 61 per cent, and after four weeks, thirty, or 73 per cent. At fourteen weeks, thirty-three, or 80 per cent, gave negative reactions to the Schick test.

Table 3 shows the results for the entire group. The number varies since it includes those who were present for all of the tests and those who were present for one or more tests. At one week, twenty-six, or 43 per cent, of sixty-one nurses, gave negative reactions, and at two weeks, twenty-one, or 41 per cent, of fifty-one nurses. The discrepancy in the expected rise in percentage was due to the comparatively large number of nurses who were unable to be present that day. At three weeks, thirty-seven, or 63 per cent, of the fifty-nine nurses gave negative reactions; at four weeks, forty-four, or 71 per cent, of sixty-two nurses, and at fourteen weeks, fifty-two, or 87 per cent, of sixty nurses.

TABLE 4.—*Series 2—Thirty-Four Nurses With Positive Reactions to the Schick Test Were Given Two Injections of 1 Cc. of Toxoid Seven Days Apart*

	30 Days*	16 Weeks
Number of nurses appearing for Schick tests	34	27
Number of nurses rendered negative to Schick test	19	23
Percentage rendered negative to Schick test	56%	85%

* The time recorded for the Schick tests indicates the time elapsed after the second injection of toxoid.

SERIES 2 (table 4).—A second series of thirty-four nurses with positive reactions to the Schick test were given two doses of 1 cc. of toxoid at an interval of seven days. Two Schick tests were made following the intradermal injections, the first thirty days after the second injection of toxoid and the second sixteen weeks after the second injection. It was desired to use this group as a control. In series 1, a total of five Schick tests were given following the injection of toxoid. It was desired to find out if the antigenic properties contained in the Schick test material would affect the end-results. In these observations (series 2) only two Schick tests were done following the injection of toxoid. At thirty days, nineteen, or 56 per cent, of thirty-four nurses gave negative reactions, and at sixteen weeks, twenty-three, or 85 per cent, of twenty-seven nurses. The results of series 1 and 2 appear to be essentially in accord.

SERIES 3 (table 5).—A third series of fifteen nurses giving positive reactions to the Schick test were given a single injection of 1.5 cc. of the same toxoid. It was desired to see whether or not a single large dose of toxoid would give satisfactory immunity. At one week, three, or 20 per cent, of the fifteen nurses gave negative reactions; at two weeks, the number of negative reactions had not increased; at three weeks, five, or 33 per cent, of the fifteen nurses gave negative reactions, at four weeks, six, or 40 per cent, and at six weeks, eight, or 53 per cent; at ten weeks, the number of negative reactions had not increased, and at nineteen weeks, eight, or 61 per cent, of thirteen nurses gave negative reactions. It is realized that the number of cases is small and should be extended.

The results of series 3 (table 5) are in accord with the previous statement that it seems probable that a total dosage of commercial toxoid that is less than 2 cc. does not give satisfactory immunization. Bloomberg and Fleming [3] and Maloney and Fraser [10] gave two injections of toxoid, the total dosage in both series being less than 2 cc. of toxoid. These observers stated that the immunity obtained was not as satisfactory as could be desired. In this series, 61 per cent of the subjects gave negative reactions to the Schick test, and in Bloomberg and Fleming's series, 68 per cent gave negative reactions. Zingher [2] stated that a single dose of 0.5 cc. of toxoid immunized 60 per cent of a series of school children in six weeks. In this series, 53 per cent were immune in eight weeks.

TABLE 5.—*Series 3—Fifteen Nurses With Positive Reactions to the Schick Test Were Given One Injection of 1.5 Cc. of Toxoid*

	1 Week*	2 Weeks	3 Weeks	4 Weeks	6 Weeks	10 Weeks	19 Weeks
Number of nurses appearing for Schick tests	15	15	15	15	15	15	13
Number of nurses rendered negative to Schick test	3	3	5	6	8	8	8
Percentage rendered negative to Schick test	20%	20%	33%	40%	53%	53%	61%

* The time recorded for the Schick tests indicates the time elapsed after the second injection of toxoid.

COMMENT

As has been stated previously, the variable factors involved in the use of toxoid for immunization against diphtheria are the time spacing of the injections and their size. It seems that the total amount of toxoid is important. In brief, a review of the literature tends to support the view that approximately 2 cc. of commercial toxoid is necessary for satisfactory immunization of a large group of subjects giving positive reactions to the Schick test. If this is acceptable, one should consider why a single injection of a smaller quantity of toxoid should at times produce a negative Schick reaction. Glenny [12] stated:

> Among the Schick positive reactors there are those who possess some small amount of antitoxin, not sufficient to suppress the Schick reaction; such persons will respond readily to the injection of toxin-antitoxin mixtures or other diphtheria antigens and become rapidly immune. Their antitoxic content is low, but the presence of some antitoxin shows that they have reacted previously to a stimulus and their power of response is high.

12. Glenny, A. T.: The Principles of Immunity Applied to Protective Innoculation Against Diphtheria, J. Hyg. **24**:301 (Dec.) 1925.

In such cases, the single dose of toxoid has probably acted as a satisfactory secondary stimulus. It is impossible to estimate the number of persons with positive reactions who at some previous time have received a primary stimulus. The primary stimulus may have been a slight infection with diphtheria. Other stimuli may play a part. At present, it may be considered that in comparison with two doses of 1 cc. a single dose of 1.5 cc. of toxoid does not give sufficient immunity to warrant its continued use. In series 3 (table 5), 61 per cent of thirteen nurses gave negative reactions to the Schick test nineteen weeks after a single injection of 1.5 cc. of toxoid. Zingher (table 1) reported that he was able to immunize 60 per cent of a series of school children with a single dose of 0.5 cc. of toxoid. This seems to indicate that children react as promptly as do adults in any series. Frankl, Herzog and Nobel [13] in 1928 immunized a group of children, giving two doses of toxoid at an interval of three weeks. Their first dose was 0.5 cc., and the second dose was 1 cc. At two weeks, 34 per cent of thirty-two children gave negative reactions; at three weeks, 60.8 per cent of sixty-nine children, and at six weeks, 93.8 per cent of ninety-seven children. The early immunity acquired corresponds with the results in my series. The later immunity in the series of Frankl and his associates is much higher. They, however, stated that 14 per cent of fifty-seven children giving negative reactions to the Schick test included in their group showed positive Schick tests on retesting at a date later than that recorded in their original report. Furthermore, thirteen cases of diphtheria developed in their entire group of 163 children with negative reactions (8 per cent). Five cases developed within twenty-one days after the first injection, and all of the cases developed within thirty-one days after the second injection. This lends further support to the belief that at least 2 cc. of commercial toxoid is necessary for satisfactory immunization. It is highly probable that the concentration of the toxoid or the size of the doses must affect the immunity acquired.

As early as 1916 Cowie [14] advised that "repeated intradermal injections of diphtheria toxin (0.00001 cc. L+ dose), when given at intervals varying from five to twelve days, provoke the formation of antibodies and in those cases already exhibiting a certain degree of immunity, bring about a definite immunity as recognized by the intradermal or Schick test." This phase was again emphasized by Glenny,[12] who stated: "The small amount of diphtheria toxin used in the Schick

13. Frankl, Herzog and Nobel: Immunization with Ramon's Anatoxin, Wien. med. Wchnschr. **78**:1155 (Sept. 8) 1928.

14. Cowie, D. M.: Observations on the Intradermal and Repeated Intradermal Injections of Diphtheria Toxin with Reference to the Schick Test, Am. J. Dis. Child. **12**:266 (Sept.) 1916.

test is enough to act as a secondary stimulus. There are Schick positive individuals who are sufficiently immune that a second Schick test given one or two weeks after the first will give a negative result, although the first test was positive." This is undoubtedly true, but it must be remembered that comparative results only are considered. In series 3, a single injection of 1.5 cc. of toxoid was given. Seven Schick tests were made at definite intervals following this single injection. My associates and I were not primarily interested in the effect of the single injection plus the antigenic action of the large number of Schick tests, but we were interested in the ultimate immunity obtained in comparison with the immunity acquired by two or more injections of toxoid. It can be concluded only that the percentage of degree of immunity following a single injection of toxoid is not as large in the group of subjects with positive reactions as that obtained by multiple injections of toxoid, regardless of the number of Schick tests made.

Cooperstock and Weinfeld [15] in this clinic have demonstrated that two injections of 1 cc. of toxoid, given at an interval of twenty-one days, will immunize 92 per cent of persons with positive reactions to the Schick test in from four to five and a half months. This work has been confirmed by Greengard,[9] who produced immunity in 98 per cent of one hundred subjects with positive reactions within six weeks, following two injections of toxoid, the dosage and interval of injections being the same as in Cooperstock and Weinfeld's series.

In my own series (tables 3 and 4) two injections of 1 cc. of toxoid were given at an interval of seven days to a group of adults with positive reactions. Negative Schick tests were obtained fourteen and sixteen weeks after the second injection in 87 per cent and 85 per cent, respectively, in two groups.

It has been pointed out by Cooperstock and Weinfeld [15] that spacing of the injections too close together may delay immunity owing to the production of the so-called "negative" or "latent" phase. Glenny [12] states that the latent period in an immune animal is only three days. The difference in the nonimmune and the immune animal is that the nonimmune animal has not at any previous time received a primary stimulus to produce diphtheria antibodies. When one considers that the toxin in a single Schick test or its presence during a slight infection with diphtheria may give rise to a primary stimulus, it is highly probable that the truly nonimmune person represents only a small fraction of the total number. One must remember that the Schick test to deter-

15. Cooperstock, M., and Weinfeld, G. F.: Rapidity of Immunization with Diphtheria Toxoid, Am. J. Dis. Child. **40**:1035 (Nov.) 1930; footnote 6.

mine whether immunization is necessary may act as a primary stimulus if the injections of toxoid are delayed long enough for the latent or negative phase to elapse. If the subjects are in the so-called immune class with a latent period of only three days, the time interval of the toxoid injections can be reduced to any period that is greater than three days. In these observations the interval was seven days.

Local and general reactions caused by the injection of toxoid have been described by numerous investigators. The experience with toxoid injections in the clinic of the University Hospital has led me to the conclusion that reactions, both local and general, are a negligible factor during infancy and childhood. It is well known that the reactions increase in frequency and severity as adult age is reached. The economic point of view is important if adults are to be immunized. Of one hundred and fourteen nurses immunized, 25 per cent were off duty one or more days. One nurse was off duty four days. The majority were incapacitated for one day only. Five per cent were reported off duty after the first injection, and 20 per cent following the second injection. In no case was the same nurse off duty following both injections. In 30 per cent of the nurses off duty there was either a personal or a familial history of sensitization. One may question a relationship.

Of eighty-six employees (ward helpers, maids, orderlies, and others) immunized, 34 per cent were reported off duty. The average time off duty was one day. Thirteen per cent were off duty following the first and second injections, respectively. Eight per cent were off duty following both injections. Among the employees, 34 per cent of those off duty were found to have either a personal or a familial history of sensitization. In our sensitization history we included a familial or personal history of asthma, hay fever, eczema, urticaria, and similar conditions. Administration of horse serum in any quantity previous to the initial Schick test was also considered as a basis for sensitization.

Local reactions or moderate general reactions were not considered, provided the person immunized was able to be on duty and discharge his or her work efficiently. The probable disability should always be borne in mind if adults are to be immunized.

CONCLUSIONS

1. Nurses and hospital employees received two 1 cc. doses of commercial toxoid with seven days between injections. Immunity, measured by a negative Schick test, was present in from 80 to 87 per cent after from fourteen to sixteen weeks.

2. Immunity, measured by a negative Schick test, was acquired rapidly. One week after the second injection of toxoid, with an interval of one week between injections, from 34 to 43 per cent of the subjects gave negative reactions; at two weeks, from 41 to 46 per cent; at three weeks, from 61 to 63 per cent; at four weeks, from 71 to 73 per cent, and at from fourteen to sixteen weeks, from 80 to 87 per cent.

3. A single injection of 1.5 cc. of commercial toxoid did not give sufficient immunity to warrant its continued use in comparison with the immunity obtained by two injections of 1 cc. of toxoid at an interval of one week.

4. Data are here presented that tend to show that it is probable that a total dosage of at least 2 cc. of commercial toxoid is necessary for satisfactory immunization against diphtheria.

MODES OF CARDIAC INSUFFICIENCY IN CHILDREN WITH HEART DISEASE

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Many children with chronic heart disease subsequent to undetected rheumatic fever are brought to the physician.[1] While the acute phases and the numerous manifestations of this condition have been repeatedly studied,[2] the end-results of the cardiac damage have received less attention. The prevalent view that heart muscle failure in childhood is similar to that found in adults is misleading.[3] The manner in which the child's heart affected by cardiovalvular disease fails must be carefully understood before therapy adequate to prevent further progress of the damage can be instituted.

In an analysis of the case histories of 185 children under 15 years of age admitted to the Montefiore Hospital and found to be suffering with chronic rheumatic endocarditis, there were 100 who showed signs of heart failure. The time spent by these children in this institution varied from one month to five years. Since the average period of hospitalization was nearly two years, an opportunity was afforded to study the development and progress of heart failure in childhood.

CAUSE OF HEART FAILURE

In each of the fifty-seven boys and forty-three girls of this series, there was involvement of the mitral valve. An accompanying aortic insufficiency was present in eighty-one children. There were six cases of associated aortic stenosis and two instances of tricuspid stenosis. In addition, ten of the children showed signs of a relative tricuspid insufficiency, while the signs of pulmonic insufficiency were present in three cases. The type of valvular lesion was found to have little effect on the mode of cardiac insufficiency. Long-standing cases of heart failure usually showed the more extensive changes in the valves.

From the Medical Division of Montefiore Hospital for Chronic Diseases, New York.

1. Clark, T.: Heart Disease, a Public Health Problem, Pub. Health Rep. **44**:2463, 1929.

2. Wilson, M. G.; Lingg, C., and Croxford, G.: Statistical Studies Bearing on Problems in the Classification of Heart Disease in Children, Am. Heart J. **4**:164, 1928.

3. Abt, I. A.: The Decompensating Heart in Childhood, Illinois M. J. **50**:135, 1926.

Recurrent attacks of sore throat were present in forty-four children, and in ten cases tonsillitis was found to be the sole etiologic factor (that could be obtained from the history) of the carditis. Yet in only three of these cases did the cardiac symptoms and signs appear within a year following the infection in the throat. Removal of tonsils following the discovery of heart disease had practically no influence on the subsequent course of heart failure. Involvement of the joints was present in sixty-nine of the children, and eleven of them had chorea as well. Thirteen of the other children had chorea without arthritic symptoms. Within one year after the onset of either one of these illnesses, 75 per cent of these children (sixty-one) showed signs of an active carditis. The remainder were free from cardiac signs for an average period of three and one-half years. In twelve cases the detection of a cardiac lesion was the first intimation that the patient was suffering from a rheumatic infection. The average age of the children at its discovery was 7 years. In five of these twelve children other signs of the rheumatic state developed later, while the remainder (seven) succumbed to their infection in a comparatively short time (three years), failing in the interim to show any other manifestation of the disease.

It has been generally accepted that children with chronic endocarditis do well until puberty, and that then the heart fails owing to the greater demands on it supposedly made at this period.[4] Heart failure in children is unlike that in adults, in that it is usually caused by reinfection. It is well known that once a child has contracted rheumatism he may continue to harbor the infection, or is made more susceptible to reinfection.[5] The children in this series had an average of five reinfections each. While any one of the rheumatic manifestations may precipitate the failure of an infected heart, the most serious, as far as the nature of insufficiency and its outcome is concerned, are the severer infections involving the pericardium and the lungs. In thirty-nine children cardiac insufficiency followed the development of pericarditis, while in thirteen cases heart failure was precipitated by a pulmonary infection usually diagnosed as bronchopneumonia. In the remainder of the children heart failure developed during the course of

4. Morse, J. L.: Heart Disease in Infancy and Childhood, Boston M. & S. J. **161**:273, 1909. Calhoun, W. C.: Course, Prognosis and Treatment of Endocarditis in Children, Am. J. Obst. **66**:478, 1912.

5. Miller, R.: Discussion on the Etiology and Treatment of Heart Disease in Early Life with Special Reference to the Prevention of Chronic Cardiac Insufficiency, Brit. M. J. **2**:702, 1923. Poynton, F. J.: Introduction to Coombs, C. F.: Rheumatic Heart Disease, New York, William Wood & Company, 1924, p. 18. Bachmann, H. A.: The Prevention of Heart Disease in Childhood, M. Clin. North America **9**:1531, 1926.

a variety of infections, chiefly reactivity of the carditis.[6] The average age at the onset of heart failure was 10 years, that is, four years after the first discovery of the cardiac damage.

While prexisting cardiovalvular disease and over-exertion are the more important factors in the heart failure of adults, reinfection of the heart and the systemic effects of the rheumatic infection play the chief rôle in heart failure in children. In the series herewith reported on, all the children had received the benefits of a prolonged period of rest in bed. The inability of the heart to resist longer was due to the rekindling of an old infection or a rapid sequence of reinfections, and not to any sudden or prolonged physical strain.

Signs of Cardiac Failure in 100 Children (Under 15 Years of Age)

Sign	Boys	Girls
Enlargement of liver	57	43
Enlargement of spleen	18	11
Congestion of lungs	15	11
Edema of lower extremities	18	21
Edema of upper extremities	3	1
Edema of face	8	8
Hydrothorax	14	12
Ascites	11	10
Auricular fibrillation	9	11
Sinus tachycardia	3	9
Bigeminal rhythm	1	2
Heart block	2	1
Gallop rhythm	2	1
Premature auricular beats	1	..
Auricular flutter	3	2
Pulmonary edema	2	7

ENLARGEMENT OF THE LIVER

The earliest physical sign of a failing heart in children with rheumatic fever is enlargement of the liver. This sign was present in all of the cases studied. It may vary from mere tenderness below the costal margin to a huge bulging liver extending to the iliac crest. A palpable liver usually appears during the third or fourth week of continued pyrexia associated with tachycardia. In children suffering from progressive heart failure followed by improvement, enlargement of the liver, though the first sign to appear, is the last to disappear. Enlargement of the liver always recurs as the earliest sign in subsequent cardiac failures, until this organ becomes so damaged that, even though the child has recovered clinically, the increased size of the liver may remain as almost the sole witness of past attacks. Enlargement of the liver, without other signs of cardiac failure, was present in twenty children, while in thirteen additional cases it was accompanied by only

6. Boas, E. P., and Schwartz, S. P.: Some Modes of Infection in Rheumatic Fever, Am. Heart J. **2**:375, 1927.

enlargement of the spleen or congestion of the lungs. Nine of these thirty-three children succumbed to the rheumatic infection within two years following the appearance of this sign of heart failure.

It appears that the infection that has gripped the child and caused the heart to fail may have attacked the liver as well. In the postmortem examination of fifteen patients in this series who died at the average age of 11½ years, the average weight of the liver was found to be 1,221 Gm. In addition to chronic passive congestion and fatty changes, there were thickening of the capsule, fibrosis and scarring. Microscopic examination showed a moderate amount of round cell infiltration in the areas of scarring. The increase in the periportal connective tissue was striking. The round cell infiltration was most marked in this area. There was an additional distortion of the liver lobule by the cells of the regenerating bile ducts scattered throughout.[7]

Ordinarily, these changes are thought to be caused by increased pressure in the hepatic veins, due to their proximity to the heart.[8] MacCallum has shown that this is a mechanical impossibility. He expressed the belief that the liver cells are destroyed by insufficient nourishment and oxygenation.[9] Many years ago, French investigators, noting that the liver became badly damaged in prolonged or repeated infections of the heart, named the resulting condition cardiac cirrhosis and tried to establish it as a pathologic entity.[10] Piéry, maintaining that prolonged stasis alone did not explain the pathologic process in cardiac cirrhosis, demonstrated the existence of an inflammatory process.[11] Clinically, the huge size that the liver attains in severe cardiac failure leads to the assumption that acute rheumatic fever produces serious injury to the hepatic cells, which are replaced by interstitial tissue, an ideal repository of fluid. A virtual edema of the organ may be present. This hepatic enlargement may recede with adequate therapy, but since the extensive damage to the liver is, to a certain extent, irreparable, the patient is markedly handicapped during subsequent infections.

The large number of cases (29 per cent) that showed enlargement of the spleen reflects on the circulatory and inflammatory changes that have occurred in the liver.

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7. Levy, J.: The Hepatic Lesions in Rheumatic Fever, to be published.

8. Kaufmann, E.: Pathology, Philadelphia, P. Blakiston's Son & Co., 1929, vol. 2, p. 890.

9. MacCallum, W. G.: Textbook of Pathology, ed. 3, New York, W. B. Saunders Company, 1925, p. 488.

10. Cornil and Ranvier: Manual of Pathological Histology, London, Smith, Elder & Co., 1886, vol. 2, p. 373.

11. Piéry, M.: De l'oedème, et de la congestion dans leurs rapports avec la production de la sclérose, Thèse de Lyon, 1899; Pathogénie de la cirrhose cardiaque, Arch. gén. de méd. **186**:582, 1900; Les données récentés sur l'étiologie et l'anatomie pathologique de cirrhose du foie, Lyon méd. **113**:997, 1909.

ACCUMULATION OF FLUID

During the prolonged episodes of rheumatic infection, other evidences of heart failure appear. Occasionally one of the earliest signs is edema of the face, accompanied at times by swelling of the hands. This edema of the face and hands occurred in acutely ill children who failed to show any evidence of nephritis. It is open to question whether such swelling of the upper portions of the body could be due to anaphylaxis. No conclusive evidence could be found to support such a view. It is interesting to note that of the seventeen children who presented this phenomenon, ten had definite evidences of a recent pericarditis. All the children had enormously dilated left auricles. It can be seen that the pressure exerted on the superior vena cava by such a dilated left auricle augmented in its mechanical effect by pericarditis could be a causative factor in this "nephritic" distribution of edema in cardiac disease in children. Recently, Elias and Feller discussed the mechanism by which this could occur.[12]

Edema of the lower extremities was present alone in sixteen cases, with ascites in seven, with hydrothorax in six and with both in eleven. Hydrothorax was present alone in seven children and with ascites in two others. Ascites occurred alone in only one case. In summary, the most usual locations of accumulation of fluid were the lower extremities (forty cases), the thorax (twenty-six cases) and the abdomen (twenty-six cases). There was no definite relationship of any one form with the other. The retention of fluid usually occurred during periods of sinus rhythm. The only constant factor in all the cases was the extensive enlargement of the liver. That the liver is of value in water metabolism is apparent from the work of Mann,[13] who showed that hepatic activity is important in the formation of lymph. Accordingly, it is not surprising that 52 per cent of the children had accumulation of fluid in the various body depots following enlargement of the liver. The presence of edema in any portion of the body is evidence of either a prolonged course of rheumatic infection or repeated seizures of heart failure.

ARRHYTHMIAS

Though Schwartz and Weiss [14] have emphasized the frequent occurrence of auricular fibrillation in children, serious disorders in rhythm

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12. Elias, H., and Feller, A.: Stauungstypen bei Kreislaufstörungen (mit besonderer Berücksichtigung der exsudativen Pericarditis), Vienna, Julius Springer, 1926, p. 220.

13. Mann, F. C.: The Relation of the Liver to Metabolism, the Harvey Lectures, ser. 23, 1927-1928, Baltimore, Williams & Wilkins Company, 1929, p. 72.

14. Schwartz, S. P., and Weiss, M. M.: Auricular Fibrillation in Children, Am. J. Dis. Child. **36**:22 (Jan.) 1928.

are still considered a rarity in childhood.[15] Nevertheless, cardiac irregularities were present in twenty-five cases in this series, the diagnosis being verified with the electrocardiograph in every case. Auricular fibrillation was the most frequent disturbance in rhythm, being present in twenty children. Although there were more boys than girls in this series, in only nine of the fifty-seven boys did auricular fibrillation develop. Lewis,[16] the first to call attention to the relative frequency of this arrhythmia in rheumatic women, thought it was due to the prevalence of mitral stenosis in this sex. In a series of thirty-five children and young adults who had this irregularity, Cookson [17] found the ratio to be three girls to two boys, the same as in the present series. When one analyzes the mode of onset of auricular fibrillation in children of the present series, it is found that in five of them the arrhythmia developed as a terminal phenomenon. In three children, auricular fibrillation followed an attack of chorea. In two of the girls, the irregularity was apparently brought about by an emotional upset in the course of a rheumatic reinfection. The continued administration of digitalis in attempts to slow the pulse rate and to secure diuretic action during the course of active carditis was the source of the arrhythmia in ten other children. Among these there were three boys and two girls in whom auricular fibrillation became the established rhythm following the administration of large doses of digitalis in order to curb the rapid rate of auricular flutter. Thus, the onset of the arrhythmia may be due to an extracardiac mechanism, the stimulus being toxic, infectious or neurogenic. Furthermore, young girls who have been subjected to attacks of rheumatic fever seem to respond to this excitant more readily with the development of auricular fibrillation.

During the recurrent episodes of rheumatic fever, nine girls and three boys had repeated attacks of sinus tachycardia. These attacks usually subsided spontaneously with the disappearance of the pyrexia and were refractory to digitalis. In fact, in one girl auricular fibrillation developed following a large dose of the drug given in an endeavor to reduce the rate. In three cases of auricular fibrillation with active carditis, the use of digitalis precipitated the inception of a bigeminal rhythm, which promptly ceased when the administration of the drug was discontinued. During active carditis, one boy showed multiple premature auricular contractions, while in three other children heart block developed. One of the latter, as well as two other children, showed a gallop rhythm as a terminal phenomenon. Since there were

15. Simpson, R. H., and Batten, L. W.: Some Points in the Diagnosis of Cardiac Lesions in Children, Lancet **2**:372 (Aug. 24) 1929.

16. Lewis, T.: Clinical Disorders of the Heart Beat, ed. 6, London, Shaw & Sons, Ltd., 1925, p. 91.

17. Cookson, H.: Auricular Fibrillation in Children, Lancet **2**:1139 (Nov. 30) 1929.

five distinct disturbances in rhythm seen in 25 per cent of the children in this series, it is evident that arrhythmias are of frequent occurrence in the failing heart in children with rheumatic fever.

PULMONARY EDEMA

A severe form of heart failure in children is acute pulmonary edema. Though it is stated to be an unusual finding in rheumatic heart disease,[18] it occurred repeatedly in seven boys and two girls of this series. In one of the latter, the rheumatic endocarditis was associated with congenital syphilis, and the second attack of pulmonary edema was the cause of death. In addition to showing marked emotional instability, all the children had very labile blood pressures and considerable variability in the heart rate. Two of the girls had sundry evidences of vicarious menstruation, and the attacks of pulmonary edema bore a more or less constant relationship to the onset of the menses. It is interesting that these were the only patients that did not show signs of edema elsewhere. Hydrothorax developed in two cases, and signs of bronchopneumonia in two others. In one girl with auricular fibrillation, the attacks of pulmonary edema occurred during periods of rapid ventricular rate.

There is considerable confusion regarding the causation of acute pulmonary edema. The question as to whether or not the branches of the pulmonary artery are under the control of the vasomotor nerves is of practical importance in this connection, for some believe that the attacks of acute pulmonary edema are reflex phenomena brought on by cardiac distention.[19] That left ventricular insufficiency is an important factor in the production of such attacks is undoubtedly true,[20] but the sudden onset, the evanescence and the frequent repetition of attacks require further explanation. Furthermore, the greater susceptibility of girls and young women, especially those with vasomotor instability, to such seizures is suggestive. Since there is definite experimental evidence showing the existence of vasomotor nerves in the lungs,[21] the attacks of acute pulmonary edema in children with chronic heart disease seem to be brought on by reflex stimulation of this system in a failing heart.

PROGNOSIS AND TREATMENT

With a mortality of 44 per cent at the average age of 11½ years, it is little wonder that the attitude toward the results of treatment is

18. Paul, J. R.: Pleural and Pulmonary Lesions in Rheumatic Fever, Medicine **7**:383, 1928.

19. Doumer, E.: L'oedème aigu du poumon dans le rétrécissement mitral en dehors de la grossesse, Arch. d. mal. du coeur **19**:791, 1926.

20. Gallavardin, L.: De l'oedème du pulmonaire aigu dans les cardiopathies valvulaires, Arch. d. mal. du coeur **14**:262, 1921.

21. Tribe, E. M.: Vaso-Motor Nerves in the Lungs, J. Physiol. **68**:154, 1914.

one of hopeless discouragement. Since twenty-two of these children died within the first year following the onset of insufficiency from a fulminating reinfection with pericarditis, the prime objects in an adequate regimen of therapy are the combating of the reinfection and the prevention of recrudescences. At present, rest combined with large doses of salicylates in the acute exudative and proliferative stages is the most approved method of attack. Discovery of an exudative pericarditis with prompt removal of the fluid may be life-saving. Prevention of reinfection entails increasing the resistance of the child with appetizing food of high caloric and adequate content as well as with fresh air and sunshine. Passive graduated exercises in bedridden patients are necessary to prevent deformity. Immunity may be attempted by desensitization with suitable antigenic substances.

That the outlook is not altogether hopeless may be garnered from the fact that fifty-six of the one hundred children are living at the time of this report, at the average age of 14 years, nearly four years after the onset of heart failure. The advantages of any form of therapy are difficult to evaluate when stress is placed on the treatment of the carditis rather than on the manner in which heart failure takes place. The most satisfactory responses to therapy are obtained during periods of apparent inactivity. Enlargement of the liver should be treated vigorously on its first appearance. The administration of dextrose may serve to prevent damage to the liver. A most effective drug for reducing the size of the liver and securing diuresis is salyrgan. The drug is more effective in children who are not having active attacks of fever.

Surgical intervention for extensive pericardial adhesions deserves considerable attention. One child in this series who had the benefit of such a procedure has remained comfortable for three years. Mechanical relief for an already handicapped heart action may result also from judicious tappings for hydrothorax or ascites. The use of the more common diuretic drugs for the removal of edema proved of little value. Pyrexia in itself appears to be an effective diuretic. Several children lost many pounds of accumulated fluid during a few days of high fever. With the onset of auricular fibrillation, digitalis is the medication of choice, but, unless carefully controlled clinically and electrocardiographically, it may produce toxic manifestations. Digitalis did not produce diuresis in children with normal sinus rhythm.[22] Occasionally auricular fibrillation may be restored to sinus rhythm by the administration of quinidine, but it is open to question whether the children are not more comfortable when they are having a slow auricular fibrillation.

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22. Schwartz, S. P., and Levy, J.: The Effects of Digitalis on the Edema of Children with Rheumatic Fever and Chronic Valvular Disease in the Presence of Sinus Rhythm, Am. J. Dis. Child. **42**:1349 (Dec.) 1931.

It is interesting that the longevity of children with auricular fibrillation was greater both in the fatal (12½ years) and in the living groups (15 years) than in those with normal sinus rhythm. Pulmonary edema is an acute episode of dire significance, and yet the children can recover. In six cases the average duration of life following the first attack was four months, while one girl lived five years after the initial attack of pulmonary edema. The most effective antidote seems to be large doses of atropine given with morphine sulphate.

CONCLUSIONS

1. Heart failure in childhood is brought on by frequent reinfections.

2. The dominant feature of cardiac insufficiency is enlargement of the liver. It may be the single sign of failure and always recurs in subsequent episodes of failure as the first sign.

3. Following the enlargement of the liver there was accumulation of fluid in the extremities, abdomen and chest. Under varying conditions this fluid may become redistributed and may cause further enlargement of the liver.

4. Auricular fibrillation is a relatively common manifestation of insufficiency in girls, but is less frequently seen in boys. Other arrhythmias, such as auricular flutter, occur in children with active carditis. Toxic manifestations of digitalis may develop, such as bigeminal rhythm.

5. Pulmonary edema of either paroxysmal or terminal nature occurs in the later stages of heart failure and, while of grave prognostic significance, may respond to treatment.

6. Adequate therapy can prolong life and partially rehabilitate the child with cardiac insufficiency.

CYANOSIS IN THE NEW-BORN

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Transient or persistent cyanosis appearing in new-born infants is not uncommon. In fact, premature infants almost invariably show slight blueness of the skin or mucous membranes at one time or another. Especially is this noted at the time of feeding, and it seems to bear out the supposition of Hess [1] that it may in part be due to a weakness of the respiratory muscles, which is exaggerated by the fatigue of nursing. Von Reuss [2] expressed the belief that in the premature child, cyanosis is due to lack of cerebral development. In the present study, however, there were definite pathologic lesions to explain the cyanosis in the premature infants as well as in those born at full term.

Lundsgaard and Van Slyke [3] have shown that the appearance of cyanosis is coincident with an oxygen unsaturation of 5 Gm. of hemoglobin. Whether the cause of this lack of oxygen is due to a circulatory disturbance, an incomplete pulmonary ventilation or a cerebral injury is often in doubt. Findings other than the cyanosis may assist in making a diagnosis. There may be evidence of pneumonia; blood-tinged fluid may be obtained on spinal puncture; or an enlarged heart with an accompanying murmur may be sufficient evidence to attribute the cyanosis to a congenital malformation of the heart. Occasionally, however, the cyanosis may be the only apparent abnormality. With this point in mind it is thought that some assistance may be gained by knowing the relative frequency of the various pathologic lesions found in infants who suffer from severe cyanosis, and who die during the first month of life.

The material for this study was obtained from six hundred consecutive postmortem examinations performed at the New York Nursery and Child's Hospital over a period of approximately five years. Practically all examinations were made by the same resident pathologist, with the result that descriptions and methods were uniform, and a more careful

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1. Hess, J. H.: Premature Infants, in Abt, I. A.: Pediatrics, Philadelphia, W. B. Saunders Company, 1923, vol. 2, p. 492.

2. Von Reuss, A. R.: The Diseases of the New-Born, New York, William Wood & Company, 1927, p. 150.

3. Lundsgaard, C., and Van Slyke, D. D.: Cyanosis, Baltimore, Williams & Wilkins Company, 1923, p. 2.

evaluation of data was possible. From this group were separated one hundred and eighteen infants who had died before 1 month of age and who had shown definite cyanosis of more than a transitory nature. No questionable cases were included, and an attempt was made to exclude those in which the cyanosis was purely a terminal manifestation.

The frequency with which prematurely born infants appeared in this selected group was to be expected. There were sixty-five of them, born three or more weeks before their expected time, each weighing less than 5 pounds (2,300 Gm.) at birth.

Injury to the brain or meninges was found more frequently than either pulmonary involvement or cardiac anomalies. As a single entity, however, pneumonia was most commonly found. It must be borne in mind that these were postmortem observations, and that undoubtedly injury to the central nervous system might produce death, whereas many infants with a mild cardiac malformation or a small pneumonic process might show cyanosis, but recover more readily.

PULMONARY LESIONS

Pneumonia among new-born infants received considerable attention from Johnson and Meyer.[4] They found it present in ninety-seven of five hundred consecutive postmortem examinations, and expressed the belief that sixty-eight of the infections were antenatal. Thaysen [5] was of the opinion that all infants dying of pneumonia within three days of birth were infected previous to delivery. Browne,[6] in his series of cases, found pulmonary infection in 26.2 per cent, and stressed the point that the patients showed little defense reaction and few physical signs. Unfortunately, none of these authors discussed the question of cyanosis to any extent. Johnson [7] mentioned it as associated with the cases that showed a hyaline membrane lining the alveolar air sacs and obstructing the terminal bronchioles. The origin of this hyaline membrane was believed to be amniotic fluid that had been aspirated some time before birth. More recently, Farber and Sweet [8] emphasized the importance of this hyaline material found in the respiratory tract of new-born infants.

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4. Johnson, W. C., and Meyer, J. R.: A Study of Pneumonia in the Still-born and Newborn, Am. J. Obst. & Gynec. **9**:151 (Feb.) 1925.

5. Thaysen, T. E. Hess: Die akuten nicht spezifischen Pneumonien der ersten Lebenstage, Jahrb. f. Kinderh. **79**:140, 1914.

6. Browne, F. J.: Pneumonia Neonatorum, Brit. M. J. **1**:469 (March 25) 1922.

7. Johnson, W. C.: Pneumonia in Newborn Infants with Lesions Resembling Influenza, Proc. New York Path. Soc. **23**:138 (Jan.-May) 1923.

8. Farber, S., and Sweet, Lewis K.: Amniotic Sac Contents in the Lungs of Infants, Am. J. Dis. Child. **42**:1372 (Dec.) 1931.

The presence of a hyaline membrane in the alveoli and terminal bronchioles was found to be much more frequent than was expected. It appeared as wavy, homogeneous, eosin-staining strands, irregularly placed on the lining membrane of the terminal air sacs and atria. It was most frequently found in a few partially distended alveoli in a region surrounded by atelectatic lung. Probably the hyaline membrane, by obstructing the small bronchioles, was the cause of the collapsed alveoli in the adjacent lung. It was found microscopically in the lung sections of eleven infants. In three it formed a definite membrane almost completely lining the air sacs. These, it was believed, were of the type

Fig. 1.—Photomicrograph, × 80, showing a bronchus completely plugged with aspirated amniotic fluid; it is chiefly made up of desquamated epidermal cells, and is surrounded by atelectatic lung.

described by Johnson, and probably the membrane was the chief factor in the production of cyanosis. The action of the membrane was similar to that of pulmonary edema, which Hoover [9] showed acted as a barrier preventing the interchange of gases between capillary blood and adjacent alveolar air. In the eight cases with a more irregular distribution of hyalin, it was probable that, here too, it played some part in the production of cyanosis, although in the microscopic sections examined the amount was insufficient to justify the assumption that it

9. Hoover, C. F.: Moisture in the Air Spaces of the Lung and Oxygen Therapy, J. A. M. A. **71**:880 (Sept. 14) 1918.

was the only factor involved. In only three of the eight infants was there any significant lesion in other parts of the body.

The presence of hyalin in the lung did not always stimulate an inflammatory reaction. In only two instances was it accompanied by pneumonia. Also, in three instances in which aspirated amniotic fluid was present, there was no inflammatory process. The absence of such a reaction may be explained in that all but one of these eleven infants died within twenty-four hours of birth.

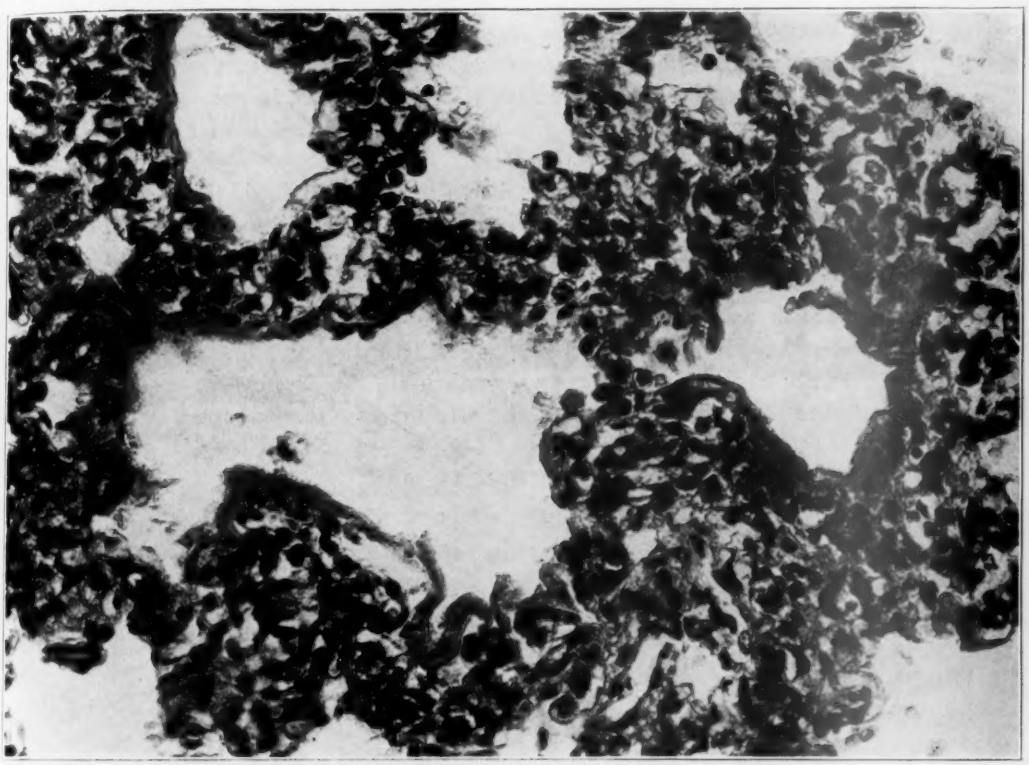

Fig. 2.—Photomicrograph, × 280, showing a hyaline membrane lining the alveolar air sacs.

Pneumonia, as it occurred, did not differ pathologically from the disease as seen in older children. There were twenty-eight cases of this type of infection. Eight showed an intracranial lesion as well as the pneumonia, although in only four was it severe. In all instances the pneumonia was probably the principal cause of cyanosis. Clinical findings were extremely variable. Rather extensive hemorrhage into the lung tissue was present in six cases, and was probably a manifestation of hemorrhagic disease of the new-born.

ATELECTASIS

It was not possible in any instance to demonstrate sufficient pulmonary atelectasis to warrant the assumption that it was the sole cause of cyanosis. According to Loewy and von Schrötter,[10] two thirds of one lung may be rendered useless by bronchial obstruction before cyanosis appears, provided the flow of blood is not interrupted. An atelectasis of this extent was not found, except in a few instances in which it accompanied other severe pathologic lesions. Kundrat [11] showed that an intracranial injury in the region of the respiratory center caused delayed alveolar expansion. In such cases the cause was primarily intracranial and not pulmonary. Holt [12] reported only twenty-five cases of severe atelectasis in 10,000 deaths. It must be remembered, however, that an atelectatic lung was the frequent location of a beginning pneumonic process.

Among the one hundred and eighteen infants examined, thirty-nine showed gross atelectasis. In most instances it was of little importance. In four cases it was severe, involving the major part of one or more lobes. In each of these cases there was also a large cerebral hemorrhage, which was most probably the primary lesion and the cause of the cyanosis. Pulmonary hemorrhage accompanying atelectasis was occasionally seen at postmortem examination. This may have contributed to the cyanosis merely by its mechanical obstruction.

INTRACRANIAL LESIONS

Injury of the brain or meninges was most often due to hemorrhage. The importance of intracranial bleeding was first stressed by McNutt [13] in 1885. Since that time many others [14] have shown the frequency with

10. Loewy, A., and von Schrötter, H., quoted by Lundsgaard and Van Slyke (footnote 3, p. 40).

11. Kundrat, R.: Ueber die intermeningealen Blutungen Neugeborner, Wien. klin. Wchnschr. **3**:887 (Nov. 13) 1890.

12. Holt, L. Emmett: Diseases of Infancy and Childhood, ed. 9, New York, D. Appleton and Company, 1926, p. 39.

13. McNutt, Sarah: Apoplexia Neonatorum, Am. J. Obst. **18**:73 (Jan.) 1885.

14. Green, R. M.: Intracranial Hemorrhage in Newborn, Boston M. & S. J. **170**:682 (April) 1914. Brady, J. M.: Lumbar Puncture in Meningeal Hemorrhage of the New-Born, J. A. M. A. **71**:347 (Aug. 3) 1918. Warwick, Margaret: Cerebral Hemorrhage of the Newborn, Am. J. M. Sc. **158**:95 (June) 1919. Conkey, O. F.: Complications of Labour: A Cause of Intracranial Hemorrhage, Arch. Pediat. **40**:239 (April) 1923. Ehrenfest, H.: The Causation of Intracranial Hemorrhage in the New-Born, Am. J. Dis. Child. **26**:503 (Dec.) 1923. Gordon, A.: Meningeal Hemorrhages in the New-Born and Their Remote Consequences, Am. J. Dis. Child. **27**:303 (April) 1924. Grulee, C. G.: Treatment of Intracranial Hemorrhage in the New-Born, J. A. M. A. **85**:336 (Aug. 1) 1925. Brandt, M. L. Intracranial Hemorrhage in the Newborn from the Obstetrician's Viewpoint, M. J. & Rec. **121**:521 (May 6) 1925.

which it occurs in new-born infants. That it may occur in apparently normal infants was demonstrated by Sharpe and Maclaire [15] and later by Roberts,[16] who found blood in appreciable quantities in the spinal fluid of 9 and 14 per cent, respectively, of new-born infants.

Pallor, rather than cyanosis, has often been emphasized as an indication of cerebral injury. This pallor, however, as Krogh [17] has pointed out, may be due to capillary constriction, and, because there is a small amount of blood in the superficial layers of the skin, may obscure a true cyanosis.

It was difficult to explain why hemorrhage occurring over the cerebral hemispheres, as it most frequently did, should cause cyanosis. Nevertheless the association was too frequently found to be dismissed.

TABLE 1.—*Relative Frequency of the Types of Intracranial Lesions and the Age of the Infants at the Time of Death*

	Hemorrhage						Tentorial Lacerations				
	Mild				Severe*		Small†		Large		
	Meningeal		Intracerebral								
	Term	Premature	Term	Premature	Term	Premature	Term	Premature	Term	Premature	Meningitis‡
Death within 24 hours of birth	5	10	..	1	5	6	6	8	5	1	..
Death 2d to 7th day (inclusive)	6	3	4	1	4	8	7	1	3	3	2
Death 8th to 30th day (inclusive)	2	2	..	..	3	5	..	3	1	1	2

* The severe hemorrhages were located as follows: Twenty were over the cerebral hemispheres; six were infratentorial; four were both above and below the tentorium, and one was intracerebral, in the temporal lobe. Ten cases showed large tentorial lacerations and are also included in that group.

† Hemorrhage accompanied twenty small lacerations.

‡ One case was accompanied by mild meningeal hemorrhage and is included in that group; another case occurred with a small laceration of the tentorium and is counted in both classes.

It must have caused pressure, directly or indirectly, on the cardiac or respiratory centers of the brain, with resulting disturbance of their

15. Sharpe, W., and Maclaire, A. S.: Intracranial Hemorrhage in the New-Born, J. A. M. A. **81**:620 (Aug. 25) 1923; Signs of Acute Proved Cases of Intracranial Hemorrhage in the Newborn, M. J. & Rec. **123**:215 (Feb. 17) 1926; Observations of Intracranial Hemorrhage in Four Hundred Consecutive Newborn Babies, J. Obst. & Gynæc. Brit. Emp. **32**:79 (Spring) 1925; Further Observations of Intracranial Hemorrhage in the Newborn; Significance of Yellow Spinal Fluid and of Jaundice in These Cases, Am. J. Obst. & Gynec. **8**:172 (Aug.) 1924; Intracranial Hemorrhage in the Newborn, Am. J. Obst. & Gynec. **9**:452 (April) 1925; Intracranial Hemorrhage in the Newborn, Surg., Gynec. & Obst. **38**:200 (Feb.) 1924; Further Observations of Intracranial Hemorrhage in the Newborn, Surg., Gynec. & Obst. **41**:583 (Nov.) 1925.

16. Roberts, M. H.: The Spinal Fluid in the New-Born, J. A. M. A. **85**:500 (Aug. 15) 1925.

17. Krogh, A.: The Supply of Oxygen to the Tissues and the Regulation of the Capillary Circulation, J. Physiol. **52**:457 (May 20) 1918-1919.

normal rhythm. Hemorrhage of a varying degree was found in sixty-five of the one hundred and three cases in which examination of the brain and meninges was permitted. In thirty-one cases the bleeding had been profuse and was probably the cause of the cyanosis. In many instances, however, it was complicated by some other intracranial injury, especially by tentorial tears.

Laceration of the tentorium, as described by Beneke,[18] was not uncommon. In a series studied by Holland,[19] it was present in 48 per cent of one hundred and sixty-seven postmortem examinations. So frequently did it occur that he stated: "Actual tear, unaccompanied by hemorrhage, cannot be considered as a fatal injury." This is probably true, since of fourteen infants in this series in which the tear extended more than half way across the tentorium, eleven showed profuse bleeding. In twenty-five others, the tears were small and there was no bleeding, so that it is probable that that laceration in no way contributed to the production of cyanosis or death.

Crothers [20] has emphasized the frequency of injury to the central nervous system following breech delivery. This was corroborated by finding tentorial tears and hemorrhage in four infants so delivered.

CONGENITAL CARDIAC DISEASE

Cyanosis directly traceable to congenital cardiac disease was not a common observation among these new-born infants. It is possible that many infants with cardiac malformations did not show cyanosis until after 1 month of age. Also some of them may have shown cyanosis, but the lesion may have been such that it was compatible with life. Such cases would not have come under examination.

The mechanical causes and the cardiac lesions most frequently associated with cyanosis of cardiac origin have been completely described by Abbott [21] and others. Whether the cyanosis was due to venous stasis caused by a pulmonary stenosis, to a "left to right shunt" through a defective septum or to a transposition of the great vessels was of little significance. A murmur may or not have been present. In this series, three infants showed an uncompensated transposition of the great vessels, one had an interventricular septal defect and another trilocular heart.

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18. Beneke: Ueber Tentoriumzerreissungen bei der Geburt, sowie die Bedeutung der Duraspannung für chronische Gehirnerkrankungen, München. med. Wchnschr. **57**:2125 (Oct. 11) 1910.

19. Holland, E.: The Causation of Foetal Death, Great Britain, Ministry of Public Health, Reports on Public Health and Medical Subjects, 1921, no. 7.

20. Crothers, B.: The Disorders of the Nervous System in Childhood, New York, D. Appleton and Company, 1926, p. 5.

21. Abbott, Maude E.: Congenital Cardiac Disease, in Osler, W.: Modern Medicine, ed. 3, Philadelphia, Lea & Febiger, 1927, vol. 4, p. 628.

Other minor anomalies were found in many cases, but their association with the cyanosis was improbable. A patent foramen ovale was so commonly seen that it could not be considered abnormal. One infant showed coarctation of the aorta, which was probably of less significance than the rudimentary lung also present. One other case worthy of note only because of the rarity of the condition was that of a premature closure of the foramen ovale. A thin membrane was completely attached at the annulus and bulged loosely into the auricle. Smith [22] has reported a similar case.

TABLE 2.—*Cardiac Lesions Found at Postmortem Examination*

Lesions	Full Term	Premature
Normal	23	31
Patent ductus arteriosus	18	20
Patent foramen ovale	2	4
Patent ductus arteriosus and foramen ovale	4	7
Transposition of the great vessels with patent ductus arteriosus	3*	..
Coarctation of the aorta with patent foramen ovale	1	..
Trilocular heart with patent ductus arteriosus	..	1*
Interventricular septal defect	1 (small)	1* (large)
Ruptured auricle	..	1
Premature closure of foramen ovale with patent ductus arteriosus	1	..

* Cases in which the lesion was probably the cause of cyanosis.

TABLE 3.—*Age at Death*

Age	Full Term	Premature
Less than 24 hours	17	25
2 to 4 days	19	12
5 to 7 days	5	6
8 to 14 days	3	9
15 to 30 days	9	13

OTHER CAUSES

The question of thymic enlargement producing sufficient pressure to cause permanent or transient cyanosis has been much disputed. In five hundred postmortem examinations, Johnson [7] found no evidence of obstruction in a single case. This observation was confirmed by the examination of the infants in this series. The average weight of the thymus was only 6.8 Gm., about one half of that which Hamman [23] considered normal for the new-born. The total weight has probably less significance than the thickness and consistency of the gland. Lateral roentgenologic examination, as devised by Pancoast and

22. Smith, E.: Premature Occlusion of the Foramen Ovale: Large Pulmonary Artery and Duct and Contracted Left Heart, Tr. Path. Soc. London **1**:25 (Dec. 7) 1846-1848.

23. Hamman, quoted by MacCallum, W. G.: Textbook of Pathology, ed. 4, Philadelphia, W. B. Saunders Company, 1928, p. 898.

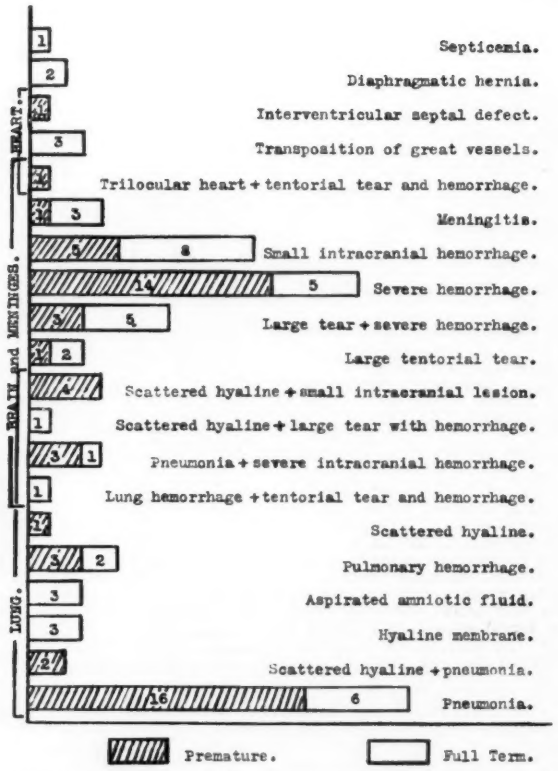

Fig. 3.—Chart showing the relative frequency of the pathologic lesions causing cyanosis.

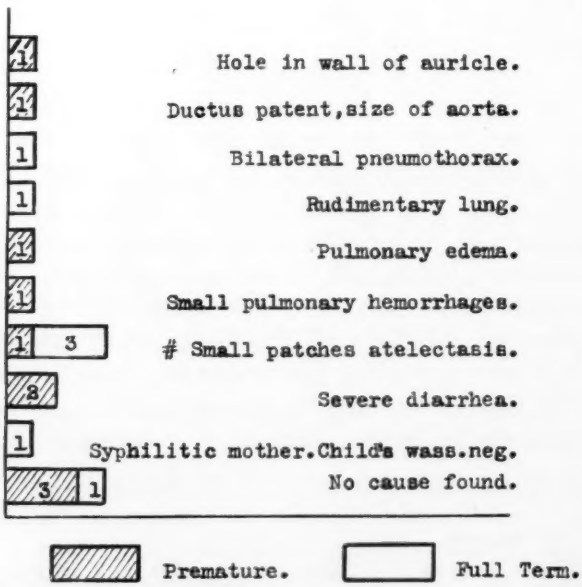

Fig. 4.—Chart showing findings in seventeen cases in which lesions were less definitely the cause of cyanosis, but probably played some part in its production. In two cases (see chart) examination of the brain and meninges was not permitted.

Pendergrass,[24] has shown the thymus to be less often the cause of tracheal obstruction than was formerly believed. It was not disputed that occasionally the thymus gland might cause sufficient tracheal constriction to produce cyanosis, but this must be rare indeed.

Diaphragmatic hernia, septicemia, including the type described as Winkel's disease, or various drug poisonings must not be overlooked as possible causes of cyanosis. These, however, are not common.

COMMENT

By analysis of the results obtained at one hundred and eighteen postmorterm examinations, an attempt has been made to ascertain the more common pathologic lesions causing cyanosis in new-born infants. It is realized that the causes of cyanosis and of death are not synonymous, and that several factors may be involved. Hemorrhage, whether intracranial, pulmonary or intra-abdominal, cannot be disregarded as a contributing cause in many instances.

Intracranial lesions, although frequently found at postmortem examination, are not always of sufficient severity to produce symptoms. Especially is this true of small tentorial tears, which must often be disregarded. On the other hand, extensive unilateral or bilateral tears of this supporting structure, accompanied as they most frequently are by profuse hemorrhage, would seem sufficient cause for cyanosis. Meningeal bleeding may occur in the absence of tentorial lesions, and is often profusely distributed over the cerebral hemispheres or at the base. These two types of lesion, namely severe tentorial tears and meningeal hemorrhage, are usually the direct result of birth trauma, hence cyanosis will appear within the first few days of life.

The cyanosis accompanying congenital cardiac disease is due to the mixture of venous with arterial blood or to stasis. With such abnormalities, the blueness may vary directly with the activity of the infant and not appear until some weeks after birth. Unless the lesion is severe, life is possible, in some cases well into childhood. The relatively few cases that appear in this series are therefore not indicative of the true frequency of cyanosis as a manifestation of congenital cardiac abnormalities.

Pneumonia is the most common single lesion found in these infants. The disease does not differ from that seen in older children, except for the variability of the signs. The appearance of a hyaline membrane, which is probably the result of aspirated amniotic fluid, is more common than was formerly believed. In small amounts, this is probably of little

24. Pancoast, H. K., and Pendergrass, E. P.: Roentgenologic Diagnosis of Diseases of the Upper Respiratory Tract in Children, Am. J. Roentgenol. **23**:241 (March) 1930.

significance. In the cases in which it forms a membrane lining the alveoli of large sections of the lung, it cannot help but cause respiratory embarrassment. Persistent cyanosis appears early in the life of these infants, and may be the only sign present.

Other pathologic conditions may produce cyanosis in the new-born, but they are relatively infrequent. The greatest difficulty in diagnosis is usually between pulmonary and cerebral lesions. Lumbar puncture or roentgenologic examination of the chest may be of assistance in establishing the cause of cyanosis, but not infrequently may give no definite aid. In the infants coming to postmortem examination, intracranial lesions, including both hemorrhage and tentorial tears, are the most frequent cause of cyanosis, but, as a single severe entity, pneumonia is the predominant factor.

161 West Sixty-First Street.

Case Reports

CONGENITAL DEFECT OF THE SKIN IN A NEW-BORN INFANT

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DODGE CITY, KAN.

The occurrence of multiple areas of defect in the skin of a new-born infant always attracts medical attention. Rather numerous reports [1] in the recent literature serve to enhance this interest, and the bizarre results of some unknown process affecting the cutaneous areas serve also to elicit considerable discussion as to causation. Lundwahl [2] has reviewed the several theories concerning etiology in a complete manner. Abt,[3] in 1917, in the most thorough report, collected thirty-six cases from the literature. According to him, rupture of inflammatory adhesions between the external layers of the skin and the amnion, the so-called Simonart ligaments or bands, could give rise to the congenital defects. Greig [4] stated the belief that it is more probable that the congenital defects arise from an arrest of development than, as has been reported, from the amniotic adhesions of the fetus.

More numerously reported as involving the head, especially the vertex, the lesions occupy other areas, including, less frequently, the knees, thighs, elbows, temporal, lumbar and axillary regions, and the bridge of the nose. In the instances of multiple defects there is, I believe, an apparent segmental symmetry, as shown by the case herein described. The punched-out circular defect of the scalp so frequently noted is also not unlike the lack of continuity of tissue that past experience has associated with trophic disturbances.

From the Dodge City Clinic.

1. Graff, E.: Congenital Aplasia of the Cutis, Zentralbl. f. Gynäk. **45**:705 (May 21) 1921. Lonne, F.: Zentralbl. f. Gynäk. **45**:1554 (illustration) (Nov. 19) 1921. Kehrer, E.: Monatschr. f. Geburtsh. u. Gynäk. **31**:183, 1910. Bais, W. J.: Nederl. tijdschr. v. geneesk. **2**:1138 (illustration) 1900. Loewy, E.: Dermat. Wchnschr. **79**:1660 (illustration) 1924. Heinrichsbauer, F.: Monatschr. f. Geburtsh. u. Gynäk. **75**:267, 1931.

2. Lundwahl, K.: Causation of Congenital Skin Defects, Arch. f. Gynäk. **130**: 487, 1927.

3. Abt, I. A.: Congenital Skin Defects, Am. J. Dis. Child. **14**:113 (Aug.) 1917.

4. Greig, D. M.: Localized Congenital Defects of the Scalp, Edinburgh M. J. **38**:341, 1931.

REPORT OF A CASE

History.—The patient was referred to me for examination by Dr. M. G. Flath of Stanley, N. D., on July 8, 1930. Birth had occurred at 4:00 a. m. on this day. Respiration was spontaneous and was sustained in a normal manner. Cardiovascular function was likewise assumed and maintained normally. The mother, a primipara, had experienced a healthy pregnancy, and labor was unattended by any untoward incident. Neither parent had ever been seriously ill, and both said that they had not had venereal infection. The maternal and paternal relatives could recall no similar or dissimiliar abnormality of the skin, and the family history was negative for any chronic metabolic affliction.

The attending physician and nurse had observed the placenta and had considered that it was abnormal in general surface contour. Circumference and weight were estimated to be within normal limits. There were areas of paler tissue, varying from 1 to 4 cm. in diameter, indiscriminately and diffusely scattered

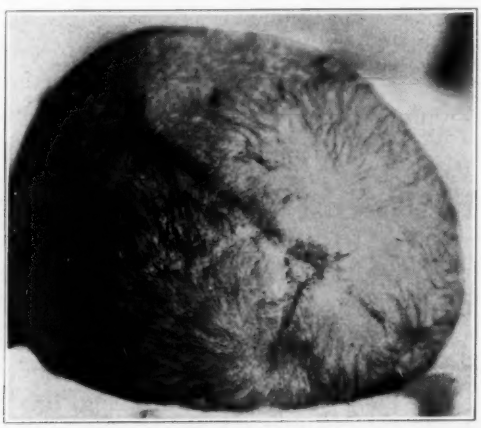

Fig. 1.—Defect of the scalp ten hours after birth.

throughout the placenta. "Areas of fatty degeneration" seemed to them best to describe the condition. Unfortunately, the placenta and membranes were inadvertently discarded.

Examination.—On examination the infant's weight was 3,260 Gm.; the circumference of the head, 35.6 cm.; the length, 50.7 cm., and the chest, 33.7 cm. The temperature was 99 F., and the pulse rate, 124.

The features were of normal contour, and the color of the skin had a normal reddish hue; the respirations were interrupted by spells of vigorous crying. The usual bodily movements were present. Urine was voided and meconium discharged. The eyes were open, and the pupils reacted equally to light. Nose, ears, mouth and throat showed no abnormality. There were no unusual signs detected in the lungs and heart. The edge of the liver was palpable 2.5 cm. below the costal margin in the midclavicular line, and the spleen was not felt. Phimosis was present, and the testicles and scrotum were normal on palpation.

Skeletal and muscular attachments conformed to standard. The knee and plantar reflexes were present and equal; the clasp reflex also was present. The

usual recoil responses to chilling of the body surface and to painful stimuli were observed. This was noticed especially when the dressings were removed from the abdomen. Urinalysis was negative; the Wassermann and Kahn reactions of the blood serum were negative. The white blood count was 11,200; polymorphonuclears, 37 per cent, lymphocytes, 55.5 per cent; monocytes, 2 per cent, and eosinophils, 5.5 per cent. The morphology was normal.

The area of defect at the vertex, of which von Reuss [5] portrayed a typical example, was much more extensive in my patient, as shown in figure 1.

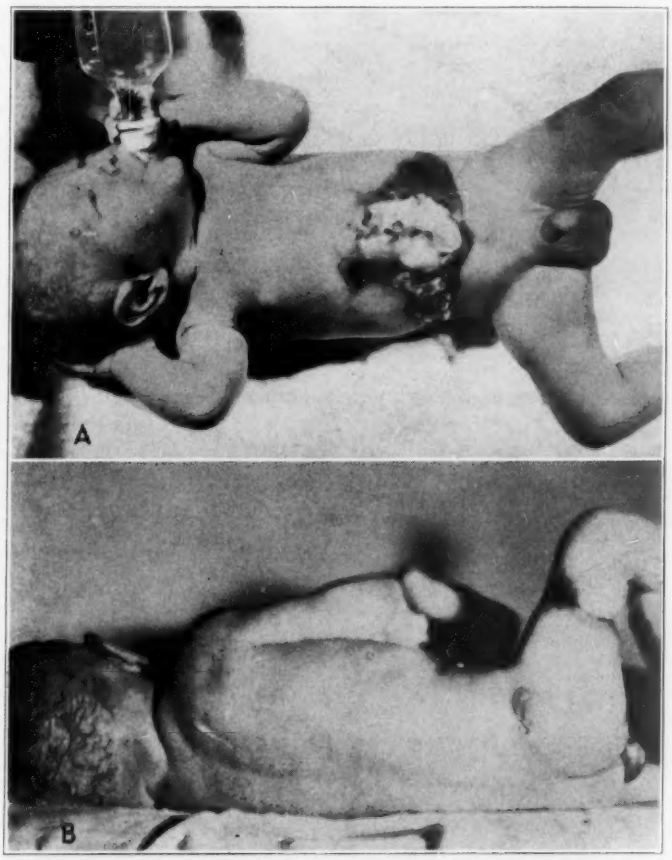

Fig. 2.—Abdominal defect (*A*) and defects of the right lumbar region and thigh (*B*) ten hours after birth.

Longitudinally, it extended over the whole vault of the cranium from a point 2 cm. anterior to the anterior fontanel to a point just anterior to the posterior fontanel. At each end it was crossed by a transversed, linear defect. A circular area 1.5 cm. at the vertex was reddish and was formed of newly developed granulation tissue.

5. von Reuss, A. R.: Diseases of the Newborn, New York, William Wood & Company, 1921, pp. 384-386.

The remainder of the defect had a fibrous and cicatricial consistency. The width of the whole I-shaped area of this newly formed scar tissue was from 1.5 to 2 cm. Greig considers the possibility that congenital defects of the hairy scalp, not extending to the bone and not associated with osseous defects, may be of two

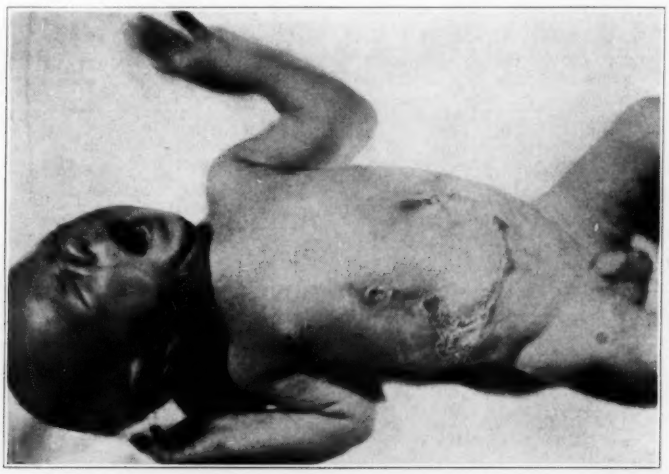

Fig. 3.—Abdomen almost completely healed three weeks after birth.

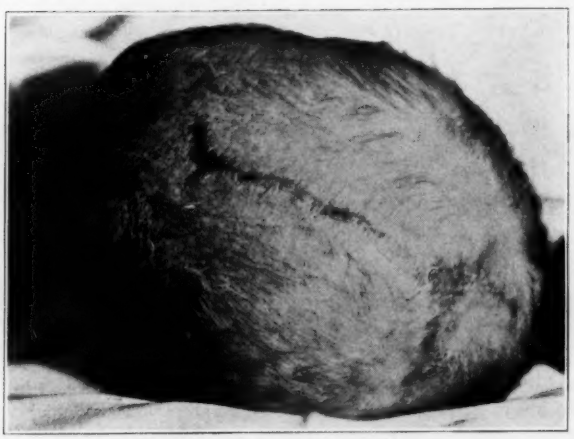

Fig. 4.—Defect of the scalp completely healed three weeks after birth.

types: one, bullous or a raw surface, and the other, membranous or cicatricial. He suggested that the types are related but dissimilar, and their coexistence unusual. From a consideration of the case reported here, it would not be erroneous to assume that the types merely represent varying stages of repair in lesions of variable extent.

The abdominal defect, as shown in figure *2 A*, was very similar to that of the patient whose case was reported by Adair and Stewart.[6] The large U-shaped area involved more than one-half the area of the abdomen and exhibited varying stages of repair. The more complete healing occurred just below and lateral to the umbilicus and in the epigastric region. The rawest surface was located in the right hypochondriac area. Immediately surrounding a normal umbilical stump was a band of healthy skin and subcutaneous tissue 2.5 cm. in width. Just above the umbilicus was a wide band of healthy and cicatricial tissue extending to the midepigastric region. In this area, normal skin and subcutaneous portions alternated with recently formed fibrous parts. The darkness of the abdomen, as noticed in figure *2 A*, was due to the loss of skin and subcutaneous tissue, and there lay on the muscle fascia a thin layer of transparent cicatricial tissue.

The involvement of each lower extremity was identical. The location of the lumbar defect was exactly at the posterior superior iliac spine, and the margins of the bone were readily palpable. It was a dimpled depression and was fibrous. Ventrally, it extended along the crest of the ilium 4 cm. Both lumbar defects were practically healed. The lesions on the thigh were also undergoing repair, though not as complete as that of the lumbar areas. The location of the defects on the leg was midway between the hip and the knee, and they extended in a linear fashion approximately half way around the leg on the posterior and lateral surfaces. There was marked grooving of the tissues of the thigh at the points of maximum repair. This was more noticeable on the right than on the left, and may be seen in figures *2 A* and *B* and 3. Cicatricial contraction of the skin and subcutaneous tissues had occurred, and the presumption is that these areas had perhaps healed because of the probable smaller extent of the lesions, and not from variable incidence.

Course.—On July 31, the infant was again brought in for examination. It was breast-fed and had gained 2,300 Gm. in weight; progress had been normal. The scalp, as shown in figure 4, plainly illustrates the circular scar at the vertex as the type of ulcer so frequently described by authors. In figure 3 it is seen that the only remaining defect was a small ulcer in the right hypochondriac region. The lateral portions of the abdomen were healed, and epithelium had encroached on the sides, so that the total area was reduced. The thigh and lumbar lesions were completely healed. The treatment given over the raw surfaces had been plain, dry dressings and a simple dusting powder.

COMMENT

In consideration of the two lumbar defects attention is directed to the dimpled "depressions" so often seen in the routine examinations of groups of children of all ages. These so-called "dimples" are usually seen more frequently at the following sites: at the acromion eminences at the shoulder, over the olecranon at the elbows and at the posterior superior iliac spines. The premise is offered at this time that these "dimples" represent completely healed areas of congenital cutaneous defect. Again the suggestion is made that, in view of the

6. Adair, F. L., and Stewart, C. A.: Congenital Defect of the Skin of the New-Born, Am. J. Dis. Child. **27**:60 (Jan.) 1924.

deep grooving of the defects of the leg, the so-called amniotic grooves that have been noticed not infrequently on the lower extremities of children may be in reality totally healed cutaneous defects. It is also evident from a study of this case that the term congenital cutaneous defect should obviously include loss of subcutaneous tissue.

SUMMARY

A case of congenital cutaneous defect with loss of subcutaneous tissue is reported.

714 Second Avenue.

DISTURBANCES OF FUNCTION OF THE SUPRARENAL GLANDS IN CHILDREN

HAROLD J. FREEDMAN, M.D.
BOSTON

Since disturbances of function of the suprarenal glands are rare in infancy and early childhood, I am prompted to report a case seen recently. The clinical picture was clearcut, although pathologic proof was absent because of unexpected clinical improvement.

REPORT OF A CASE

History.—A girl, aged 6 months, was admitted to the Boston Dispensary on Dec. 2, 1930, with the chief complaint of blood in the stools on three occasions in the preceding two months.

Nothing relevant was found in the family history. The mother and father were living and well; the mother was 19 years of age, and the father was 25. There had been no other pregnancies. The child had red hair, but there was no other known incidence of red hair in the family through either the maternal or the paternal grandparents. The child had been delivered at full term with low forceps. There was difficulty in getting the child to breathe, but there were no convulsions, hemorrhage or paralysis. The birth weight was approximately 7 pounds (3,200 Gm.). The baby was breast fed for one month, and then, because of failure to gain normally, she was weaned, and a milk-water-sugar formula was prescribed.

I saw the child for the first time when she was 2½ months old, and her weight was 8 pounds (4,100 Gm.). Because of the history of severe intestinal disturbances, characterized by marked diarrhea with large green or clay-colored stools and loss of weight, my impression was that celiac disease was present. It was found that the diarrhea could be stopped by a fat-free diet with calcium caseinate, but severe diarrhea was again precipitated by even small increases of fat or starch. At the age of 6 months the child weighed 10 pounds and 5 ounces (4,730 Gm.), and was taking a skimmed-lactic-acid-milk formula, clear soups, beef juice and egg yolk. She had had no diseases except occasional rhinitis, and at the age of 6 months had no teeth, did not sit up, did not smile or follow objects, and appeared underdeveloped mentally. A small amount of free blood was noted on the outside of one of the stools two months before admission. For one day one month before admission, free blood was noted on all of the stools. Once more, the day before admission, blood was seen on all of the stools.

Examination.—On physical examination it was noted that the patient was small for the age of 6 months and that her hair was abundant, silky and reddish golden. She was fairly well developed and well nourished. The head was small, and the fontanels were open with no bulging or depression. Examination of the

From the Department of Pediatrics and the Department of Clinical Research of the Boston Dispensary.

Fig. 1.—Pigmentation of the left leg and left buttock.

Fig. 2.—Pigmentation of the face, right arm, right anterior portion of the thorax and both legs, and prominence of the breasts.

Fig. 3.—Pubic hair and prominent labia.

eyes, ears, nose and throat gave negative results. The thorax showed a marked rosary. The lungs and heart were normal. The abdomen was protuberant, and considerable gas was present. The liver was not felt, but the edge of the spleen was just felt at the costal border. There was definite hypotonicity of all muscles. There was hair on both cheeks, fuzz on the upper lip, generalized fuzz on the body and a moderate amount of hair on the back and on the vulva. The clitoris was visible and palpable, and was almost 1 cm. long. The labia majora and labia minora were hypertrophied. The skin showed a small amount of brownish pigmentation on the face and considerable pigmentation on the back of the left leg and left buttock. Blood, which did not clot, was coming from the vaginal orifice.

A roentgenogram of the skull, made on December 4, suggested microcephaly. The sutures were not so much expanded as they should be at the age of 6 months. There was no evidence of increase of intracranial pressure and no localized signs of tumor. A barium enema, on December 4, showed no evidence of megacolon. Slight redundancy of the sigmoid was observed; the ascending colon and cecum did not fill well. On April 9, 1931, the blood was found to contain 3,780,000 red cells and 10,150 white cells per cubic millimeter. A differential count showed 43 per cent polymorphonuclear leukocytes, 42.5 per cent lymphocytes and 10 per cent monocytes. The Hinton test for syphilis in both mother and child was negative. The Mantoux tuberculin test was negative. Repeated metabolism tests were unsatisfactory. The Aschheim-Zondek test, performed on August 1 (one week before menses), showed no excess of anterior lobe pituitary in the urine. On rectal examination, on the same day, the body of the uterus was felt to be normal in size and on a plane with the cervix. Dr. W. H. Grant, of the Gynecological Department of the Boston Dispensary, performed the Aschheim-Zondek test and also palpated the child's uterus, which he believed to be of normal size.

Because of improvement in the child's well-being and growth, and because of the diminution of symptoms, operative intervention was not considered advisable.

Course.—Since the patient's first admission to the dispensary, she has had several more menstrual periods, all enduring from two to three days, and except for a lapse of four months (from the age of 7 to 11 months) these periods occurred regularly about four weeks apart. Figures 1, 2 and 3 show the appearance of the child at the age of 11 months. The diet was steadily built up until, at the age of 14 months, she was being fed a diet normal for her age, and she weighed over 20 pounds (9,000 Gm.). The pigmentation at first deepened in intensity and spread over both cheeks, the lower part of the back, the buttocks, the legs and the arms. Later, however, the extension of the pigmentation stopped, and the hair on the scalp changed from the previous reddish golden to dark brown. The child showed marked improvement in both mental and physical development, although definite hypotonicity of all musculature remained. At the age of 14 months she could stand, speak a few words and respond in a normal fashion to her environment. The blood pressure on several occasions did not reveal hypotension, the systolic pressure being at all times high, between 90 and 95, and the diastolic between 50 and 60.

COMMENT

Celiac disease or chronic intestinal indigestion with intolerance to fat and sugar seems well established in the case reported. The question is whether there is an endocrine disorder of some sort. Certain symptoms lead to the supposition that various glands may be involved. The early appearance of both primary and secondary mature sex attributes

suggests that pathologic changes exist in one or more of the several glands controlling sex function. It is well known that certain tumors, since they occur in the developmental period of life, are associated with striking general abnormalities which may consist of precocious sexual maturity or unusually rapid somatic growth. It is especially tumors of the pineal gland, the gonads and the suprarenal glands that are associated with this syndrome. By reviewing the literature of cases in which the situation of pathologic changes has been determined either by operation or by necropsy, I hope to be able to demonstrate the probable position of abnormalities in the case reported.

Tumors of the Pineal Gland.—I have found only nine tumors of the pineal gland reported in the literature. With one exception they have all been in boys, and in all instances height was excessive and physical development rapid. There is, therefore, no apparent reason for considering the condition in the reported case as one of involvement of the pineal gland.

Tumors of the Gonads.—One would expect that tumors of the ovaries or testes would have an influence on somatic and sexual development. The number of cases found in the literature, however, is small, only twenty in all, and in nineteen of these the patient was a girl. Neurath [1] reported three cases of ovarian tumor. In one case menstruation began at 19 months, and death occurred at 21 months. Adult breasts and pubic hair were present. Glynn [2] reported a case of menstruation at 4 years in which the menses stopped after removal of an ovarian tumor. Riedl [3] and Gaudier [4] each reported a case of menstruation at 4 years; in both cases menstruation stopped after the removal of ovarian tumors. Krewitz [5] reported a case of adenocarcinoma of the ovary; the patient was a girl aged 5 years whose menses had begun at the age of 2 years.

I quote these several reports to emphasize the fact that the premature onset of the menstrual cycle points to pathologic involvement of the ovaries. However, Jaffe and Marine [6] found definite enlargement of the ovaries of rabbits that survived double suprarenalectomy. This

1. Neurath: Die vorzeitige Geschlechtsentwickelung, Ergebn. d. inn. Med. u. Kinderh. **4**:46, 1909.

2. Glynn: The Adrenal Cortex, Its Rests and Tumors; Its Relationship to Other Ductless Glands and Especially to Sex, Quart. J. Med. **5**:157, 1912.

3. Riedl: Menstruatio Praecox und Ovarialsarkom, Wien. klin. Wchnschr. **17**:942, 1904.

4. Gaudier: Tumeur solide de l'ovaire chez une enfant de quatre ans, Bull. et mém. Soc. de chir. de Paris **34**:712, 1908.

5. Krewitz: Adeno-Carcinoma of the Ovary in a Five Year Old Girl, Illinois M. J. **37**:407, 1920.

6. Jaffe, H. L., and Marine, D.: The Influence of the Suprarenal Cortex on the Gonads of Rabbits, J. Exper. Med. **38**:93, 1923.

indicates that there is a close relationship between the suprarenal cortex and the gonads in the female. I believe that this is of importance in view of the premature appearance of the menstrual cycle in the case reported.

Tumors of the Suprarenal Glands.—In a review of the literature I found only thirty-two cases of tumor of the suprarenal cortex, twenty-six of which I shall consider in the present paper. Such tumors lead to remarkable sex anomalies. They may take various forms. One form is pseudohermaphroditism in which the internal genitalia are female but the external genitalia, voice and bodily conformation approach the male type. Pubertas praecox, adult virilismus and hirsutismus also may result from tumors of the suprarenal cortex.

Hoskins [7] described three types. In the first type, suprarenal hypernephroma occurs during fetal life, and pseudohermaphroditism is a result. However, the internal genitalia may be hypoplastic. In the second type, suprarenal hypernephroma occurs in early postnatal life, and a condition of pubertas praecox may arise. Although this may be unnoticed in earlier months or years, later all changes may take place, such as abnormal accumulations of fat on the hips, lower part of the abdomen and mons veneris. Rapid growth and increasing strength may be noted. The intellect may or may not be affected. All the phenomena of puberty begin to develop rapidly, so that at the age of 5 or 6 years full sexual maturity may be attained. The third type results from suprarenal neoplasm appearing after puberty. This may result in virilismus or hirsutismus. Girls between the ages of 15 and 20 years are most often affected. The symptoms may be expressed as menstrual irregularity, gastro-intestinal disturbance and increased physical strength.

Glynn,[2] in 1912, reported five cases of hypernephroma and reviewed twelve that had been reported previously. Kennedy and Lister,[8] in 1927, in a review of the literature, found twenty-five cases, a summary of which follows: There were twenty girls and five boys. The onset varied from birth to 13 years. The duration of symptoms before death varied from six months to fourteen and a half years. The greatest age attained was 16 years, in which case symptoms had been of six years' duration. In all cases pubic hair was present, and in twelve cases hair existed on the face. Obesity was present in eleven cases. Six of the girls had definite hypertrophy of the clitoris. The mentality of five of the girls was classified as precocious, and of three as normal; in the other twelve cases mentality was not mentioned. In relation

7. Hoskins, R. G.: Hypergenitalism and Hypogenitalism, in Abt, I. A.: Pediatrics, Philadelphia, W. B. Saunders & Company, 1924, vol. 4, p. 745.

8. Kennedy and Lister: Lancet **2**:749, 1927.

to the case presented, it is interesting to note that the earliest menstrual cycle reported started at 10 years. Two of the boys showed marked hypertrophy of the genitalia. Mentality was mentioned in four of the boys; in two it was classified as precocious and in two as normal. Great muscular development was present in three of the five boys. Operation was performed on eleven patients, of whom nine died. Fifteen necropsies were performed; in five of these metastasis to the liver was shown; in three metastasis to the lungs, and in two metastasis to both lungs and liver. All of the tumors proved to be hypernephromas.

Special attention is called to two cases. In one case, reported by Schiff,[9] in 1918, the patient was an intelligent girl of 2 years who had an abnormally adipose face and neck, hypertrichosis, moderate beard, hair on the labia majora, normal breasts and bulging abdomen. A tumor was felt in the right upper quadrant of the abdomen. Operation revealed a hypernephroma. In the other case, reported by Harris and Plewes,[10] in 1930, virilismus was present in a child 3 years old, who presented a large clitoris, husky voice and pubic hair. Operation revealed hypernephroma. Two months later there were slight growth and improvement in the voice.

Fordyce and Evans,[11] in 1929, reported two cases of suprarenal virilismus, in one of which there were enlargement of the penis, increase in strength and the appearance of a diffuse brownish rash or pigmentation at the age of 5 months. Operation revealed an encapsulated tumor in the left suprarenal capsule. Death followed twelve hours after removal of the tumor. No spermatozoa were found in the freshly cut section.

Clearly, in these cases appearing in young boys, the virilismus is not associated with sexual precocity in the sense of potency. Although secondary sex changes were common in the girls, there was no change in primary sex function, except the questionable early menstruation in one girl of 10 years. When sex abnormalities occur in a child or a young woman, there is usually a unilateral malignant neoplasm of the suprarenal cortex.

Addison's Disease.—In association with involvement of the suprarenal cortex, there has been reported the appearance at times of generalized brownish pigmentation or the deposit of melanin in the scalp, producing red hair. This condition, described so well by Addison, is char-

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9. Schiff, E.: Premature Development of Secondary Sexual Characteristics in a Two Year Old Girl, Due to a Hypernephroma of the Right Suprarenal Capsule, Jahrb. f. Kinderh. **87**:519, 1918.

10. Harris, G. W., and Plewes, D. F.: Hypernephroma with Virilismus in a Child Three Years of Age, Canad. M. A. J. **23**:244, 1930.

11. Fordyce, A., and Evans. W. H.: Virilismus with Report of Two Cases, Quart. J. Med. **22**:557, 1929.

acterized by insidious onset, muscular weakness, pigmentation, digestive disturbances, nervous disturbances and arterial hypotension. The prognosis is poor; the natural course is usually progressively downward, with acute exacerbations at irregular intervals. Addison's disease frequently is associated with tuberculosis, although other conditions may involve the suprarenal cortex and may cause pigmentation. Any pathologic lesion that destroys the suprarenal glands will produce the characteristic syndrome in part or in whole.

Cavengt,[12] in 1921, reviewed the condition in infants. His three patients died and were apparently tuberculous. Morabito,[13] in 1927, in his article on Addison's disease in infancy, remarked that Addison's disease is rare in infancy, probably because the suprarenal glands possess special resistance to tuberculous infection and to other processes that lead to this disease. Snell and Rowntree,[14] in their study of Addison's disease at all ages, agreed that tuberculosis is the principal factor in the production of Addison's disease. However, only about a third of their patients had clinical evidence of tuberculosis. They also stated that trauma may be a factor. In twenty-six of the thirty necropsies done in their cases, caseating tuberculosis of the suprarenal glands was revealed. In four there was simply atrophy of the glands. Snell and Rowntree concluded their article with the statement: "The treatment of Addison's disease has always been a thankless and difficult task." They did, however, obtain relief or cessation of symptoms in some of their cases for as long as from five to eight years with organotherapy. Rowntree and Pfeiffner,[15] after an exhaustive survey of organotherapy, came to the conclusion that specific treatment has yet to prove its value. However, Hartman, Aaron and Culp,[16] in their article on the use of cortin in Addison's disease, concluded that the results obtained proved the value of cortin as a specific therapeutic agent in the treatment of this disease. Because of this conclusion, the child in the case reported in this paper was recently started on a regimen of suprarenal cortin. I am as yet unable to state any opinion concerning the value of this preparation.

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12. Cavengt: A Study of Addison's Disease in Infants, Pediatría españ. **10**: 161, 1921.

13. Morabito: Addison's Disease and Its Indistinct Forms in Infancy, Pediatria **35**:969 (Sept.) 1927.

14. Snell, A. M., and Rowntree, L. G.: Clinical Experiences with Addison's Disease, Ann. Int. Med. **3**:6 (July) 1929.

15. Rowntree, L. G., and Pfeiffner: Experiences in Treatment with Various Suprarenal Preparations, J. A. M. A. **96**:231 (Jan.) 1931.

16. Hartman, F. A.; Aaron, A. H., and Culp, J. E.: The Use of Cortin in Addison's Disease, Endocrinology **14**:438 (Nov. and Dec.) 1930.

SUMMARY

Hyperpigmentation, with red hair, gastro-intestinal symptoms, asthenia and muscular weakness, suggests disturbance of the function of the suprarenal glands in the case reported. Unusually early menstrual periods occurring for four months and then stopping indicate transient irritation of the ovaries. Hypertrichosis, hirsutismus, hypertrophy of the labia, hair on the mons veneris and hypertrophy of the clitoris, with symptoms characteristic of the addisonian syndrome, point to involvement of the suprarenal cortex. Because of the child's apparent improvement and well-being and the high mortality of surgical intervention, exploratory operation has not been deemed advisable. Should recovery take place without surgical intervention, it may well be that some undiscovered cause, possibly in the anterior lobe of the pituitary gland, has exerted a temporary irritation of a toxic sort on both the ovaries and the suprarenal cortex. Should surgical intervention be resorted to at some later date, the observations may be of sufficient interest to warrant a further report.

POSTVACCINAL ENCEPHALITIS ASSOCIATED WITH DIABETES INSIPIDUS

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The word "polyuria" as used in this article means excessive urination following or accompanying excessive intake of water by mouth, a "urina potus" in which the constituents of the urine remain in normal proportion to each other, but in which the urine is extremely dilute.

REPORT OF A CASE

History.—James G., aged 7½ years, had been under my supervision from the age of 18 months to 5 years, at which time the family moved east. There was nothing unusual in his early history, except a mild facial eczema.

I next saw him on May 8, 1931, when he was brought back for examination because of the following complaint:

On Sept. 9, 1930, he was vaccinated on the arm with a glycerinated vaccine virus[1] by the multiple puncture method. He had never previously been vaccinated. The third day after vaccination he had a temperature of 102 F., and a pustule developed at the site of the vaccination. The temperature returned to normal in twenty-four hours, and the child appeared well. His brother was vaccinated at the same time, but no "take" occurred. On the seventh day after vaccination the patient complained of headache and had a fever. The temperature was not taken. He had severe chills which shook the bed that night and every night for the following month, and an enormous thirst immediately developed, the child rising as many as twelve times a night to drink and urinate, drinking as much as 12 ounces (354.8 cc.) and urinating up to 18 ounces (432.3 cc.) at a time. A marked change in behavior took place; the boy, who formerly was an even-tempered, agreeable child, became difficult to manage, and showed pronounced emotional instability.

The temperature subsided in twenty-four hours, but the thirst, frequency of urination, chills and irritability continued unabated for a month, when the chills diminished in frequency; they have continued to do so up to the time of writing, though he still wakes occasionally and complains of being cold. His average twenty-four hour intake of water during the first month of illness was 220 ounces (6,505.4 cc.), and the urinary output was 185 ounces (5,470.5 cc.) (figures given by the family).

One cubic centimeter of solution of pituitary was given hypodermically three times a day in September, 1930, with no perceptible change in the intake of fluid or the output of urine.

Examination.—When brought to me on May 6, 1931, the boy weighed 51 pounds (23.1 Kg.) and was 47½ inches (120.65 cm.) tall. Physical examination

1. Manufactured by Parke, Davis & Company, Detroit.

showed a well nourished child, who in spite of the fact that he knew me well seemed very apprehensive. On removal of his clothes he started to shiver and complain of being cold, and although the room was warm, erection of the papillae (cutis anserina) appeared all over his skin, which assumed the usual color and roughness of goose-flesh, and his lips and finger-nails appeared moderately cyanotic. With the exception of equal but greatly exaggerated tendon, biceps, triceps, achilles and patellar reflexes, the remainder of the examination gave negative results. A roentgen examination of the skull revealed no pathologic change. Urinalysis gave the following results: color of water; specific gravity, 1.000 at 70 F.; an acid reaction, and no albumin, sugar, diacetic acid or acetone. The centrifugated sediment contained occasional white blood cells. The intake of fluid during twenty-four hours at this time was 256 ounces (7,569.9 cc.), the output 224 ounces (6,623.68 cc.); the average amount voided at a time was 16 ounces (473.12 cc.). Urinalysis showed normal relative proportions of the urinary constituents, but excessive dilution. The specific gravity of the urine voided in twenty-four hours was: 4 p. m., 1.002; 12 midnight, 1.001; 2 a. m., 1.003; 7 a. m., 1.000; 12 noon, 1.000 at 70 F. Results of an examination of the blood was as follows: white blood cells, 8,500; polymorphonuclears, 30 per cent; small lymphocytes, 52 per cent; large lymphocytes, 8 per cent; eosinophils, 6 per cent, and basophils, 4 per cent; the hemoglobin (Dare) was 67 per cent.

Course.—For the following two days, the child was given 1 grain (0.065 Gm.) of a barbital derivative three times a day, and as a result the intake and output of fluid was cut almost exactly in half, the average intake for twenty-four hours being 144 ounces (4,258.08 cc.) and the output 120 ounces (3,548.4 cc.). The third day 1 cc. of pituitary was instilled into the child's nostrils every four hours. The patient protested against the treatment; it was nevertheless continued. The result was a severe nervous reaction, a chill that night, complaints of severe headache and a doubling of the intake and output of fluid. The treatment was then discontinued. All these complaints vanished in the next twenty-four hours, and on returning to the treatment with the barbital derivative the intake of fluid for twenty-four hours dropped to 144 ounces, and the output to 118 ounces (3,489.26 cc.); the specific gravity of the urine was 1.004 at 70 F. The boy continued to be given this treatment and was under observation for two weeks. At the end of that time, May 20, 1931, he had gained 2 pounds (0.9 Kg.), and his appetite was decidedly improved. He has not missed a day in school during the fall, 1931. He is emotionally much more stable and has gained 4 pounds (1.8 Kg.) and grown 2 inches (5 cm.) in the past year. His intake of fluid and urinary output at present average 160 (4,731.2 cc.) and 140 ounces (4,139.8 cc.), respectively. The specific gravity now varies from 1.005 to 1.006 at 70 F.

COMMENT

This case appears to fall into one of two categories: idiopathic diabetes insipidus, which by chance was concomitant with vaccination, or postvaccinal encephalitis, with diabetes insipidus as a sequel. That this case is idiopathic is possible but not probable.

The cause of diabetes insipidus is uncertain. Generally speaking, it is a disease of young persons. There seems to be some indication of a familial predisposition. The pathologic process of the disease is also uncertain. By some authors, disturbance or disease of the pars intermedia of the pituitary is held responsible, by others the tuber cinereum

is believed to play a part. Primary polyuria may be induced by injury to the fourth ventricle in some animals, by stimulation of the third ventricle and by stimulation of the splanchnic sympathetics. Schäfer [2] found that injection of solution of pituitary produced an increase of urine. Cushing,[3] basing his conclusion on experiments, expressed the belief that disturbance of the posterior pituitary lobe is one cause of diabetes insipidus. Erich Meyer [4] said that he thought it is due to functional inability of the kidneys to excrete urine of normal concentration, while Forschbach and Weber [5] stated the opinion that it is the result of stimulation of the kidneys from the intake of abnormal quantities of substances that are excreted in the urine. Diabetes insipidus may follow the infectious fevers, such as typhoid, typhus, diphtheria, measles and scarlet fever. The recent work of Kaufmann and Gottlieb,[6] demonstrating the nerve endings in the renal epithelium, may eventually aid in the understanding of diabetes insipidus. The mechanism of the disorder is not yet understood.

In the case presented there is no family history of urinary disorder or disease of any kind. The boy had had no illness in the previous year. The polyuria and polydipsia began suddenly, with fever, headache and chills, on the seventh day following a successful vaccination with a glycerinated vaccine of calf lymph. A marked change took place in the child's disposition. He was irritable, his temper was uncertain, and emotional rages would develop on slight provocation. The vasomotor system showed pronounced change, and the tendon reflexes were all symmetrically and markedly exaggerated.

The boy has continued to improve in general health and disposition, though the urinary symptoms have improved very slowly. It seems

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2. Schäfer, Edward A. S.: An Introduction to the Study of the Endocrine Glands and Internal Secretions, Stanford University, Calif., Leland Stanford Junior University publ., 1914. Schäfer, E. A. S., and Herring, P. T.: The Action of Pituitary Extracts upon the Kidney, abstr., Proc. Roy. Soc., London **77**:271, 1905-1906. Magnus, R., and Schäfer, E. A. S.: The Action of Pituitary Extracts upon the Kidney, J. Physiol. **27**:9, 1901.

3. Cushing, H. W.: The Pituitary Body and Its Disorders: Clinical States Produced by Disorders of the Hypophysis Cerebri: An Amplification of the Harvey Lecture for December, 1910, Philadelphia, J. B. Lippincott Company, 1912.

4. Meyer, E.: Bemerkungen zu der Arbeit von Forschbach und Weber: Beobachtungen über die Harn- und Salz- Ausscheidung im Diabetes insipidus, Ztschr. f. klin. Med. **74**:352, 1912.

5. Forschbach and Weber: Beobachtungen über die Harn- und Salz-Ausscheidung im Diabetes insipidus, Ztschr. f. klin. Med. **73**:221, 1911. Forschbach: Zur Frage des Konzentriervermögens der Niere beim Diabetes insipidus, Ztschr. f. klin. Med. **77**:153, 1913.

6. Kaufmann, J., and Gottlieb, R.: The Innervation of the Renal Parenchyma, Am. J. Physiol. **96**:40 (June) 1931.

reasonable to expect that improvement will continue as long as the encephalitic symptoms continue to recede.

The average time of onset of postvaccinal encephalitis is given by the League of Nations Commission on Smallpox and Vaccination [7] as from nine to thirteen days, but may vary from two to thirty-one days. In reviewing the literature, I found only one case with urinary symptoms.[8]

Serious sequelae of vaccination against smallpox are receiving considerable attention at present, particularly abroad, where the number of cases of postvaccinal encephalitis has reached a high figure, particularly in Holland. Comparatively few cases have been reported in the United States and Canada. Viets and Shields [9] reported three cases in 1931. The first fatal case was reported by Wilson and Ford.[10] Other fatal cases were reported by Hassin and Geiger,[11] Wilson and Ford [10] and Fulgham and Beykirch.[8] Tuthill [12] reported one case, and Holbrook [13] five cases in 1930. Wolf and Brahms [14] reported one case with recovery. Defries and McKinnon [15] reported no cases in Canada up to 1929.

This case is placed on record because of the probability that it is a case of postvaccinal encephalitis with apparently diabetes insipidus as a sequel.

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7. Health Publications, League of Nations, 1928, vol. 3, p. 12.

8. Fulgham, J. H., and Beykirch, J. G.: Postvaccinal Encephalitis, J. A. M. A. **92**:1427 (April 27) 1929.

9. Viets, H. R., and Shields, W.: Vaccinal Encephalitis, Report of Three Cases, New England J. Med. **204**:10 (March 5) 1931.

10. Wilson, R. E., and Ford, F. R.: Nervous Complications of Variola, Vaccina and Varicella, with Report of Cases, Bull. Johns Hopkins Hosp. **40**:337, 1927.

11. Hassin, G. B., and Geiger, J. C.: Postvaccinal (Cowpox) Encephalitis, Arch. Neurol. & Psychiat. **23**:481 (March) 1930.

12. Tuthill, Ruth: A Case of Encephalitis and Influenzal Pneumonia Following Vaccination, Arch. Neurol. & Psychiat. **24**:759 (Oct.) 1930.

13. Holbrook, C. S.: Encephalitis and Encephalomyelitis Following Vaccination Against Smallpox, South. M. J. **23**:696 (Aug.) 1930.

14. Wolf, H., and Brahms, W. A.: Post Vaccinal Encephalitis, J. Nerv. & Ment. Dis. **71**:714 (June) 1930.

15. Defries, R. D., and McKinnon, N. E.: Post Vaccinal Encephalitis, Canad. M. A. J. **21**:516, 1929.

Progress in Pediatrics

CAUSES OF DEATH IN STATUS LYMPHATICUS

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In the realm of medicine and surgery there are still a number of pathologic conditions of uncertain etiology but none that possesses more features of interest than the condition of constitutional hypersusceptibility known as status lymphaticus. Not only is the etiology of this condition uncertain, but the symptoms are vague, the diagnosis is difficult or impossible to make, the treatment is of doubtful value, and the sudden death that is occasionally seen has never been satisfactorily explained. The interest that has been attached to this subject is evident in the enormous amount of conflicting literature that has accumulated, especially on the significance of the enlarged thymus gland. With such diversity of opinion regarding status lymphaticus and the thymus gland, it is not surprising to find some physicians who seriously question the existence of such a condition and the occasional sudden death without adequate cause. In a recent contribution,[1] I attempted, in a correlation of many known facts resulting from clinical, experimental and postmortem experience in this whole subject, not only to establish more firmly status lymphaticus as a definite pathologic condition but to emphasize its importance to the medical world in general because of its frequent occurrence, in various degrees, causing a lowered resistance and hypersusceptibility in many persons, especially infants and children. In this review, I shall attempt to explain the causes of the deaths which have been of such startling suddenness and about which so many opposing theories have been advanced.

THEORIES OF DEATH

The sudden death of a person without adequate cause has been observed, of course, for many years, and it is likely that in ancient days such a death was often attributed to divine intervention without an attempt being made to establish a cause. In this scientific age, however, one is not content to accept such a phenomenon without an adequate

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1. Campbell, E. H.: The Relationship Between Status Lymphaticus, the Thymus and the Suprarenal Glands, Arch. Otolaryng. **15**:517 (April) 1932.

explanation, and it is therefore to be expected that many theories have been advanced to account for these fatalities.

Apparently the earliest writer to attempt an explanation of these deaths was Kopp,[2] who advanced the view that the enlarged thymus, which had been found associated with such deaths since Felix Plater first reported a case in 1614, caused pressure on the trachea, great vessels and autonomic nerve trunks. Since then this pressure theory of death has been rather commonly believed and has been supported by such careful observers as Noback [3] and Jackson,[4] in spite of the fact that other careful observers, after considerable experimental and clinical study of the thymus, have emphatically denied that pressure from an enlarged thymus could compress the trachea to such an extent as to cause death.

Paultauf [5] was one of the earlier writers to attempt to explain these deaths as due to heart failure. He regarded the death as a consequence of cardiac inhibition resulting from destroyed equilibrium between the tonus of the sympathetic and that of the vagus nerves. His theory also took into consideration the deficiency of the chromaffin system which had been observed in these cases.

The theory of hypersusceptibility to physical and chemical agents, as a cause of death, has been advocated by Kundrat [6] and Blake.[7]

Solokoff, cited by Cavengt,[8] explains the sudden termination as due to a disturbance of calcium metabolism, with sodium ions predominating in the blood, which leads to a fatal spasm of the glottis. This has received little or no support from others. Another theory that has gained but little credence is that compression of the trachea or nerves causes a reflex inhibition of the heart or of respiration.

Symmers [9] believes that death can be explained by anaphylaxis, sensitization and shock resulting from the liberation of nucleoproteids from the widespread follicles of the thymus.

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2. Kopp, J.: Oenkwürdigekeiten in der arzlichen Praxits, Frankfurt- am-Main, Hermann, 1830, vol. 5; quoted by Marine.

3. Noback, G. J.: Contribution to the Typographic Anatomy of the Thymus Gland, Am. J. Dis. Child. **22**:120 (Aug.) 1921.

4. Jackson, C.: Thymic Tracheostenosis, Tracheoscopy, Thymectomy, Cure, J. A. M. A. **48**:1753 (May 25) 1907.

5. Paultauf, A.: Neben die Beziehungen der Thymus zum plö.zlichen Tod, Wien. klin. Wchnschr. **2**:877, 1889.

6. Kundrat, R. V.: Wien. klin. Wchnschr. **8**:1, 26 and 64, 1895.

7. Blake, J. A.: Surgical Aspects of Status Lymphaticus, Am. J. Surg. **35**: 745, 1902.

8. Cavengt Gutiérrez, S.: La endocrinologie en relacion con la patologia infantl, Pediatria españ. **9**:45, 1920.

9. Symmers, D.: Status Lymphaticus, Am. J. Dis. Child. **14**:463 (Dec.) 1917.

Some authors, such as Hart [10] and Wooley,[10] have sponsored the internal secretion theory of the thymus, assuming death to be due to an oversecretion having a toxic action on the myocardium. Such a theory can have little or no weight, since no internal secretion from the thymus has ever been discovered and the most reliable experimental data places the thymus in the group of lymphoid structures and not in the class of endocrine glands.

Mosher [11] has pointed out the similarity between death from acidosis and death from status lymphaticus. He feels that some fault in the chemistry of food will be found eventually to be at the bottom of the condition.

There have been several advocates of the theory that death is due to cerebral hemorrhage from a rupture of hypoplastic cerebral arteries. This theory without doubt explains many of the sudden deaths.

Other theories that may be only mentioned are: 1. Death follows suprarenal exhaustion and hemorrhage from a vessel into the suprarenals or ventricles of the brain. 2. Death is the end-result of intoxication from products of faulty metabolism. 3. Death is due to an abnormal thymic secretion of a general lymphotoxemia.

Last to be mentioned is the old theory of Wiesel,[12] who believed the cause of death to be an insufficiency of the suprarenal glands. He suggested that there was a sudden fall of blood pressure due to hypoplasia of the chromaffin tissues of the suprarenal glands which resulted in insufficient production of epinephrine. This deficiency led to a sudden increase in the tonus of the vagus with cardiac dilatation. He observed that in cases of status lymphaticus the medulla of the suprarenal glands showed almost complete absence of chromaffin staining, and this observation, according to Tracy,[13] has been confirmed by Hedinger, Hart, Bartel, Warthin and others. This theory is by far the most important of all in the explanation of these sudden deaths, and it has been greatly strengthened in the last few years by the experimental data that have been accumulating on the functions of the suprarenal glands and their relationship to status lymphaticus.

THREE MAIN CAUSES OF DEATH

From the information now available, many of the old theories can now be abandoned and serious consideration given to only a few as

10. Cited by MacLean, A. B., and Sullivan, R. C.: Am. J. M. Sc. **171**:659, 1926.

11. Mosher, H.: Clinical and Preoperative Study of the Thymus in Children of the Tonsil and Adenoid Age, Laryngoscope **36**:1, 1926.

12. Wiesel, J.: Zur Pathologie des chromaffinen System, Virchows Arch. f. path. Anat. **176**:103, 1904.

13. Tracy, E.: The Mechanism of Death in Status Lymphaticus, M. J. & Rec. **2**:126, 1927.

concerned in the cause of death in cases of status lymphaticus. These are: (1) suffocation from the pressure of an enlarged thymus on the trachea or nerve trunks in the mediastinum; (2) apoplexy from the rupture of a hypoplastic cerebral vessel, and (3) by far the most important, heart failure due to an insufficiency of the suprarenal hormones.

Pressure of an Enlarged Thymus.—A brief consideration of the first of the causes will show that, while probably rare, death from pressure of an enlarged thymus does occur. That the enlarged thymus can cause sufficient pressure on the trachea to cause suffocation has been emphatically denied by many interested in this subject. However, to deny that such a condition could occur would be to contradict the direct evidence of one of our most reliable observers, Chevalier Jackson,[14] who stated that over three hundred patients who were observed bronchoscopically showed compression and the purely mechanical character of wheezing, dyspnea and impending asphyxia from thymic pressure. In 1915, he made the following statement, "Thymic death under anesthesia attributed to status lymphaticus and hyperthymization of the blood are nothing more nor less than arrested respiration due to obstructive pressure of the enlarged thymus." He mentioned that after death the engorgement factor is not evident. In a recent personal communication, Dr. Jackson stated that he had not found any reason to change his opinion that thymic death under anesthesia attributed to status lymphaticus is a purely mechanical condition resulting from compression of the trachea.

This theory has not been generally accepted, and while it is possible that it may account for an occasional death, it appears almost certain that it does not account for death in typical cases of status lymphaticus. It seems hardly conceivable that the thymus can become engorged with blood to an extent to overcome the resistance of the trachea to compression, with resultant collapse. To accept this one must assume that the pressure of the blood in the relatively small arteries supplying the thymus is sufficient to overcome the resistance of the trachea with its cartilaginous walls. Such an assumption cannot be seriously considered. It is of interest in this connection to note that Schule, according to Ray,[15] has shown that it actually requires a weight of 1,000 Gm. to close an infant's trachea.

While it is difficult to see how an enlarged thymus can produce sudden death by compression of the trachea, it is not so difficult to understand how a true hyperplasia of thymic tissue can compress a trachea and even enlarge so much as to obliterate the air space, producing a

14. Jackson, C.: Peroral Endoscopy and Laryngeal Surgery, St. Louis, Laryngoscope Company, 1915.

15. Ray, H. M.: Status Lymphaticus, Arch. Int. Med. **2**:941 (March) 1929.

slow suffocation, but not sudden death, which is seen in typical cases of status lymphaticus. It is much more easy to understand how the enlarged thymus can produce suffocative symptoms and perhaps death by compression of the vagus or the vulnerable recurrent laryngeal nerves. Compression with paralysis of the latter would, of course, result in such an adduction of the vocal cords that death from suffocation might quickly occur. Some of the deaths of children and infants with cyanosis and dyspnea can be explained, I believe, by this glottic spasm from paralysis of the recurrent laryngeal nerves and more rarely perhaps by compression of the trachea. However, this mechanical death is entirely different from the death from status lymphaticus that occurs without the cyanosis or dyspnea of the type previously mentioned.

Rupture of Hypoplastic Cerebral Vessels.—Death from rupture of a hypoplastic cerebral vessel in these cases is probably much more common than is generally believed. The fact that autopsy permits so often do not include examination of the brain causes this condition to be overlooked in some of these cases. One of the chief anatomic characteristics of status lymphaticus found at autopsy is the small heart and thin walled vessels. In the group of cases studied at the Bellevue Hospital, Zeek [16] found the heart unusually small in 51 per cent of cases and the vessel walls exceedingly thin in 26 per cent. She reported two cases of sudden death in persons with the status lymphaticus picture that were due to hemorrhage from ruptured cerebral vessels.

According to Symmers,[17] the cerebral vessels, especially the arteries entering into the formation of the circle of Willis and the branches which emerge therefrom, are often small in caliber and extremely thin and delicate. Microscopic examination reveals simple hypoplastic alterations in these vessels, the deficiency being most marked in the muscular coat. In his review of 249 cases of status lymphaticus that came to autopsy at the Bellevue Hospital, he found seven cases in which death was due to spontaneous rupture of a hypoplastic cerebral artery, all of them in patients under 30 years of age and none presenting syphilitic or precocious arteriosclerotic changes in the vessels of the brain or elsewhere.

Deaths in status lymphaticus attributable to this cause could no doubt be greatly increased if more complete and accurate postmortem examinations were made. The hypoplasia of the cerebral vessels in these cases is of great importance, as it is a constant menace to the life of a subject and may become of medicolegal importance in cases in which apoplexy is precipitated by an injury that ordinarily would be regarded as insignificant.

16. Zeek, Pearl: Vascular Hypoplasia in Status Lymphaticus, Arch. Path. **6**:1058 (Dec.) 1928.

17. Symmers, D.: Status Lymphaticus, Am. J. M. Sc. **156**:40, 1918.

Insufficiency of Suprarenal Hormones.—While perhaps many cases of sudden death can be explained by the suffocation or apoplexy theory, by far the most important cause in status lymphaticus is heart failure due to the chemical and anatomic changes incident to insufficiency of the suprarenal hormones. Marine [18] has stated that the immediate cause is stoppage of the heart, as pointed out by Pott, Eschevich, Griffith and many others. "These authors assume the existence of a neurosis of some sort in which hyperexcitability of the vagus, coupled with a weakness of the sympathetic system—autonomic imbalance—is present and is the basis of the cardiac stoppage." There appears to be no doubt that in these cases the actual cause of death is failure of the heart, but I do not believe that the basis of it will be found in any alteration of the nervous mechanism of the heart. The basis lies deeper, in the unusual properties of the heart muscle and especially in the intricate factors attendant on the initiation and propagation of the heart beat.

Tracy [18] stated that in death from status lymphaticus, the heart is found invariably in diastole, and this has been the common finding of many others. Tracy asserts that death is due to a lack of epinephrine in the blood stream, and bases his belief on the assumption that stimuli passing over the vagus fibers, in the presence of epinephrine, would cause the heart to go into systole; but in the absence of epinephrine it would fail to go into systole. Therefore, in status lymphaticus in which there is a deficiency of epinephrine, he believes that there is not sufficient of this hormone to keep the heart contracting. Such a theory will not bear close analysis, for it is common knowledge that the nervous mechanism of the heart has little or nothing to do with the initiation, propagation or continuity of the heart beat.

However, it will be found by careful reasoning that the suprarenal insufficiency with the resultant deficiency of epinephrine in circulation is of considerable importance in the fatal termination of these cases. Are there any factors in this decreased supply of epinephrine that could explain a stoppage of the heart in diastole? I believe that it can be explained by a reference to certain facts brought out by Cannon [19] in 1914. He stated that muscular exertion, asphyxia and such emotions as fear, rage and pain are accompanied normally by an increased discharge of epinephrine into the blood and by the freeing of stored glycogen from the liver for circulation through the body as dextrose. Cannon stated that observations made in their laboratory showed that the latent period of suprarenal secretion, when the splanchnic nerve was stimulated below the diaphragm, was not longer than sixteen seconds.

18. Marine, D.: Status Lymphaticus, Arch. Path. **5**:661 (April) 1928.

19. Cannon, W. B.: Emergency Function of the Adrenal Medulla in Pain and the Major Emotions, Am. J. Physiol. **33**:356, 1914.

He quoted MacLeod as asserting that within a few minutes after splanchnic stimulation the sugar in the blood rises between 10 and 30 per cent. It is a well known fact that muscles work preferably by using the energy stored in sugar, that muscular labor will greatly reduce the amount of circulating sugar, and that the increase of blood sugar greatly augments the ability of the muscles to continue contracting.

It has been observed by many experimenters that suprarenalectomy causes considerable muscular weakness, and that the muscles stimulated after suprarenalectomy were much more easily exhausted than when stimulated before this procedure. From further experimentation on fatigued muscles Cannon [19] inferred that: "Adrenalin set free in the blood prepares fatigued muscles for better response to the nervous discharges sent forth in great excitement," and drew the conclusion that "adrenalin, when freely liberated in the blood, not only aids in bringing out sugar from the liver's store of glycogen but also has a remarkable influence in quickly restoring to fatigued muscles, which have lost their original irritability, the same readiness for response which they had when fresh." Furthermore, it is a well known fact that epinephrine has a vasodilator, not a vasoconstrictor, effect on the arteries of the heart. In these facts, together with the autopsy observations of a hypoplastic heart and blood vessels and the clinical findings of hypoglycemia, lowered alkaline reserve and deficiency of suprarenal hormones in cases of status lymphaticus, there is enough material to explain the sudden deaths.

TYPICAL CASE OF DEATH

As an example, let a typical case of death occurring during anesthesia be taken. The patient with status lymphaticus that has been unrecognized possesses, as has been so often verified by autopsy, an enlarged thymus and lymphoid tissues, a small heart, hypoplastic arteries showing an especial thinness of the muscular coat, and hypoplastic suprarenal glands. When the anesthetic is begun, the child is in a state of considerable emotional excitement, and this, with the increased muscular exertion attending early anesthesia should call forth an increased output of epinephrine in the circulation. This, in turn, should set free glycogen in the liver to circulate as dextrose to supply food for the overexerted heart muscle. Because of the suprarenal hypoplasia, an increased output of epinephrine cannot be forthcoming, and so there is not an increased output of glycogen for the overly active muscle; there is not the fatigue-relieving property of the action of the epinephrine directly on the heart, and there is not the dilatation of the coronary arteries to supply more blood to the heart muscle. The heart, which is already in a weakened condition as evidenced by its hypoplastic state, rapidly uses up its store of glycogen and that availa-

ble in the blood, which has also been depleted by the increased general muscular exertion. Finally, the heart muscle has not enough food and energy to continue contracting and therefore stops in a dilated state or diastole. The existence of hypoglycemia in these cases is not an assumption but a fact, as was proved by MacLean and Sullivan,[20] who estimated the blood sugar in three cases of status lymphaticus immediately before death and found it to be considerably below normal.

While explaining these sudden deaths by an insufficiency of epinephrine in an emergency, the writer has not overlooked the fact that it is the internal secretion of the cortex of the suprarenal glands that is now considered the essential, in fact, the life-saving element of these glands. Moreover, autopsy records and the observations of a number of experimenters have shown that cases of status lymphaticus reveal a hypoplasia of the suprarenal cortex as well as evidence of a deficiency of the medullary portion. Without doubt, the signs and symptoms of status lymphaticus, particularly the lowered resistance and hypersusceptibility, are due more to a deficiency of the cortical hormone than to a deficiency in the medulla, but such patients live indefinitely until either the cortical tissue becomes too deficient and they die as does a patient with Addison's disease or until an emergency arises when an increased secretion of epinephrine is needed and found lacking. In this connection, it is of interest to observe that Bornstein and Grennels, according to Brenner,[21] have shown that at least one fourth of the suprarenal cortex must remain for life to continue.

FACTORS IN THE INITIATION AND MAINTENANCE OF THE HEART BEAT

The aforementioned explanation of death places the cause as a failure of the cardiac muscle to continue contracting owing to exhaustion and lack of food. While this may explain many of the cases that occur under rather prolonged emotional or physical energy, it will not fully account for many other deaths of greater suddenness, such as those immediately following a plunge in cold water, a hypodermic injection or a mild electric shock. For an explanation of the sudden stopping of the heart in such cases as these, I believe that it is necessary to consider the intricacies of the chemical properties and electrical reactions of cells, which are assumed to be the important factors in the initiation, propagation and maintenance of the heart beat.

A mass of experimental evidence tends to prove definitely that the heart beat originates in the sino-auricular node which is located just

20. MacLean, A. B., and Sullivan, R. C.: Blood Sugar and Status Thymicolymphaticus, Am. J. M. Sc. **171**:659, 1926.

21. Brenner, O.: Addison's Disease with Atrophy of the Cortex of the Suprarenals, Quart. J. Med. **22**:121, 1928.

below the fork formed by the junction of the upper surface of the auricular appendix with the superior vena cava. It is of interest to note that normally this area of the auricle has been found to contain a high percentage of glycogen. From this node the beat is transmitted uniformly over the muscular tissue of the auricle to reach the auriculoventricular bundle. Strong evidence has been found that the beating power is inherent in the muscle fiber itself and is independent of nervous structures. Evidence also strongly favors the theory of the propagation of the heart beat along the muscle fibers and not nerve fibers.

It is of importance now to consider the fundamental cause of cardiac rhythm, which will be found to be due to the generation of electrical impulses. Andrus and Carter [22] have shown that all known phenomena of cardiac rhythm can be satisfactorily explained by considering that they are due to the rhythmic building up and discharge of a potential difference across a semipermeable membrane.

To understand this it is necessary to consider the means by which there is a regulation of the hydrogen ion concentration of the cells and the fluids that bathe these tissues. This regulation is fundamentally of a physicochemical nature, dependent on the interaction of alkalis and acids, of which carbonic and phosphoric acids are the most important. Such acids as these possess the property of maintaining the reactions of the tissues or fluids tolerably constant when they are present in a solution which also contains an excess of their salts. However, it has been found that if ten times as much free carbonic acid as bicarbonates is present, the hydrogen ion concentration will be fifty times that of neutrality, and if there is ten times less carbonic acid than bicarbonates present, the hydrogen ion concentration will be only half of neutrality. Therefore, it is apparent that the amounts of bicarbonates and carbonic acid present in the tissues and fluids have an important bearing on the hydrogen ion concentration and the building up of potential difference between cell and fluid. Acid phosphate is the other important acid that acts like carbonic in maintaining neutrality. While the blood plasma contains much less of phosphate than bicarbonate, the tissues contain normally a considerable amount of the former, which aids them in maintaining their neutrality.

The source of the acid and basic substances concerned in these reactions is partly exogenous and partly endogenous. The exogenous source is the basic and acid substances present in the food. The amount of these can be largely controlled by the amount of sodium bicarbonate and ammonium chloride administered. The endogenous source depends on the constant production in metabolism of acids such as carbonic, phosphorous, and sulphuric and of alkalis such as ammonia and fixed

22. Andrus, E. C., and Carter, E. P.: Science **58**:376, 1923.

alkali. Carbonic acid is produced in large amounts in normal metabolism, and is excreted in a gaseous condition through the lungs. Variation in its formation and excretion is the most important factor in controlling temporary changes in the hydrogen ion concentration.

It has been found that within the muscle cells of the heart, hydrogen ions are being constantly set free so that their concentration is greater than in the fluids which bathe them where it is normally fairly constant because of the buffer salts (bicarbonates and phosphates) present. This difference in hydrogen ion concentration on the two sides of the semipermeable membrane (cell wall) will lead to electrical discharges that set up the current of action necessary for initiating the contraction of the heart muscle.

Thus the heart beat is originated and maintained but the cardiac rhythm is subjected to frequent changes, as would be expected from the frequent variations in the chemical factors present. The rhythm may be altered greatly, for instance, by the degree of permeability of the membrane, which is readily affected by changes in the concentration of the sodium, potassium and calcium on one or the other side of the cell wall. Difference in potential across the membrane may also be altered by a change of the hydrogen ion concentration of the fluid bathing the cell. Thus a decrease of the hydrogen ion concentration of these fluids has been found to slow the heart beat and an increase to quicken it.

Another important factor in regulating the hydrogen ion concentration in muscle tissue is the formation and neutralization of lactic acid. The most important chemical change in the muscles, including the cardiac, during contraction, is the appearance of lactic acid which is formed from the glycogen present in the muscle tissue. Fatigue of muscles has been found to be due to the accumulation of lactic acid in the muscle substance, and muscles stop contracting when lactic acid concentration reaches a certain fixed maximum. Lactic acid will not remain normally in muscle tissue for any length of time, because it is rapidly neutralized by the bicarbonates and phosphates in an oxidative process. It has been further found that lactic acid in the muscle cells alters greatly the relative concentration of the hydrogen ion on the two sides of the membrane (cell wall). The presence of lactic acid is therefore important in altering the hydrogen ion concentration between the muscle fibers and the fluids bathing them, so that an electrical discharge is produced that can stimulate muscular contraction.

For the heart to beat normally, therefore, a proper proportion of chemical substances in the muscle tissue and fluids is essential. In the condition of status lymphaticus in which there is considerable alteration in these chemical elements it would not be surprising to find factors present that could materially derange the normal contracting elements of the heart. In status lymphaticus there is a deficiency of two of these

chemical substances so important to muscular activity. One is glycogen and the other the bicarbonates. The deficiency of these two substances, the interference with the formation and neutralization of lactic acid in the muscle tissue, the decreased supply of suprarenal hormones and the lessening of the blood supply of the heart incident to the suprarenal insufficiency are all factors that may so alter the hydrogen ion concentration of the muscle tissues and fluids that the difference in electrical potential is lost and the stimulus for muscle contraction is absent, resulting in a stoppage of the heart.

The practical application that may be made from these deductions is naturally the restoration so far as possible of the normal chemical composition of the body tissues and fluids. The administration of bicarbonates, phosphates and dextrose and the administration of suprarenal gland products, if available, would seem to be the logical method of combating such a condition. The routine administration of sodium bicarbonate and dextrose prior to operative procedures would therefore appear to be a practical way of safeguarding, to some extent, the occasional patient that may be the victim of status lymphaticus. Other features in the treatment in such cases will be considered in a later contribution.

SUMMARY

1. Many theories have been advanced to explain the cause of death in cases of status lymphaticus.

2. Only three of these are worthy of consideration, namely: (*a*) suffocation from the pressure of an enlarged thymus on the trachea or nerve trunks in the mediastinum; (*b*) apoplexy from the rupture of a hypoplastic cerebral vessel; (*c*) heart failure due to an insufficiency of the suprarenal hormones.

3. The last of these is by far the most important. It explains the sudden death as due to the chemical and organic changes induced by the insufficiency of the cortical and medullary hormones from the suprarenal glands.

4. The chief chemical factors concerned in sudden heart failure are those that cause a disturbance in the chemical properties and electrical reactions of cells that are assumed to be the important factors in the initiation, propagation and maintenance of the heart beat.

5. In cases of status lymphaticus there is a deficiency of some of the important chemical elements that normally tend to establish contractility of the cardiac muscle, and this deficiency so alters the composition of muscle tissues and fluids that the electrical stimulus for muscle contraction may suddenly become lost, resulting in stoppage of the heart.

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THE PROMISE OF PSYCHIATRY

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My speaking before this society in some sort of answer to Dr. Brennemann's paper on "The Menace of Psychiatry" [1] was decided on with full realization that about all that I could say was "Amen." Also, there is in the audience the chairman of a committee on the relationship of psychiatry and psychology to the practice of pediatrics.[2] Moreover my title "The Promise of Psychiatry," was taken much more with an eye to some literary setting off of Dr Brennemann's article than with the slightest notion that there is any such promise—or, if there is one, that psychiatry can meet its note before being engulfed in bankruptcy.

While I can attest that these manifold misgivings were communicated to your secretary, they admittedly were not displayed until after the acceptance of your courteous invitation had been irrevocably nailed down. If what I have to say is but half the masterpiece of Machiavellian literature that was my letter of acceptance, you will be softly lulled into the startling belief that black is white, and, what is more, that psychiatry in reality has much of real and constructive value to offer to you. For with these misgivings on the subject, I yet sincerely welcomed the opportunity of discussing with you some of the difficult questions that face all of us.

To some extent you will expect me to answer Dr. Brennemann's article. When one so heartily agrees, that is a difficult assignment. In general, one has the impression that Dr. Brennemann is chiefly worried about the menace of everything in general, nor is it entirely clear just why he unloads at the door of psychiatry all of those ills that come from the following of false gods. One's bank balance in these days tells one that everything is topsy-turvy. One's neighborhood in these days tells one that there is an unnatural overemphasis on the thoughts, the doings and the spontaneous development of the child. This generation had "discovered the child" quite regardless of the

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Read at a meeting of the New England Pediatric Society, Boston, Feb. 26, 1932.

1. Brennemann, Joseph: The Menace of Psychiatry, Am. J. Dis. Child. **42**:376 (Aug.) 1931.

2. Much of the material in this paper was included by Dr. Bronson Crothers in his report on this subject at the White House Conference on Child Health and Protection.

psychiatrist. Common sense tells one that human nature seizes the concrete, the apparently definite, whenever it can and that vitamins, weight charts, sex, intelligence quotients—anything that has a name—will be caught as the focal points of interest whenever this is possible. That is of the general cussedness of the beast. Nor is there anything in Dr. Brennemann's paper to disabuse one of the doubt as to whether for every 100 persons there is any higher incidence of cussedness among psychiatrists than there is among, let us say, pediatricians, for example.

Seriously, I do not feel called on to discuss the general state of affairs. I can bring myself easily to quite the same lugubrious attitude on the matter that is expressed in Dr. Brennemann's paper. This is, however, not germane to the subject in hand.

Thus, having with one gulp swallowed Dr. Brennemann's article in toto and with one other wave regurgitated the entire mass, one is ready to start afresh.

Perhaps one could think of 1890 as commencing the present era of laboratory medicine and the golden period of specialization. Much has been written of the old family doctor previous to that time. Actually, I suppose that we know very little about him. We are wont to invest him with that same halo of perfection that, as parents, we bestow on our own childhood days. Undoubtedly he lived in a period in which most communities had but few well educated or well informed persons. It rather comfortably followed that to him were taken a great number of problems beyond the merely physical—psychologic problems, social problems. In all probability he was thus forced to view persons as actually living in a real world of social stress. In all probability, too, he understood these matters more clearly than his contemporaries, with, perhaps, the exception of the lawyer and the minister. Just how this old family doctor would measure up in days when the newspaper, the radio and the chain store university have carried information to all is problematic.

Then, approximately in 1890, medical men became much preoccupied with minutiaé. The work of the bacteriologists quite reoriented the physician. If he had previously thought of the individual as an operating unit, he quickly gave up the heresy. Life was in terms now of the bacillus, of the Widal reaction, of the Wassermann test, of the exact character of the degeneration of certain brain cells. The psychiatrist, sequestered in the mental hospital, awoke to that great new vision, the symptom complex. Hours were spent in determining whether a depression was retarded or anxious in character. The patient was but one of the white sorting cards. One punched holes here and there to indicate the presence of discrete, well described symptoms, and then,

by putting the whole in the sorting machine of the staff conference and having the said staff conference solemnly revolve twice and once stand on its head—presto! out fell the patient as dementia praecox, manic-depressive psychosis or what not. That great and revered leader, Dr. Southard, had a system of "diagnosis by exclusion." There were but ten general forms of mental aberration. All that was necessary was that one prove that the patient did not fit any of nine types, and that gave the diagnosis—he must be of the tenth! I am not here to cavil at those pioneers. Today they would be the first to be reaching toward other levels. They, and their work, were of the necessity of pioneering. I do not laugh at them any more than would you at those of your great leaders who spent countless hours over percentages of whole milk and the whole business of formulas.

I saw, three weeks ago, a little 10 year old lad who himself illustrates the period of which I am speaking. He is a befreckled, red-headed soul of better than average intelligence for whom some intra-uterine matter managed to produce a cruelly malformed left hand. Otherwise he is about as nice a specimen as you would want to see. After a time of talking of school and home and play we came to the hand. "But nobody knows about that; I always keep it in my pocket," said the child. Here, then, is not a patient who is a boy. This is a hand, albeit with a boy attached. The town where he lives, Essex County, the State of New Jersey—all these are no more than a million eyes that must not see that hand! Football? School? Marbles? O yes, he enters into all of these things with the longings and drives of any normal boy. but they are no more than the hand that must be hidden. Similarly, perhaps you have heard of so-called families that are not families, that are but puppets jiggling to the manifold strings of an enuresis problem in one of the children. And often the benighted specialist has solemnly, with his wise methods of control, but added more strings that the puppets can dance the more gaily.

There is one point that I wish to make as to this first step. This is that in a new development the pioneers seize always on the concrete. The first steps in the development of modern medicine were characterized by an insistence on the concrete *at that level.*

Owing to various factors, a change occurred. In every branch of medicine there developed the realization that the organ was but a part of a whole person. The biologist who had earlier thought that he could see life in the isolated cell began to realize that it was only as that cell interacted with others that it expressed the more real and sincere parts of its actual being. The pediatrician began now to think of the entire child. He recognized that matters of general appearance and of general ability to adapt were of importance. It is my concep-

tion of pediatrics that it has to some extent taken this second step. I hear a good deal about the general well-being of the youngster. I have even heard at your meetings about a *regimen of life,* some realization that the whole economy of the body is involved in various conditions. I hear a little less about circumcision as a cure for enuresis or masturbation and more about general measures employed, even, be it said, such matters as might enlist the cooperation of the child. An outstanding pediatrician recently said to me: "I insist that the child shall know why he is getting up at night, shall be thoroughly awakened. I have the child get out of bed himself, get his own bathrobe and slippers, close his own window, etc." Of course, either all of his children have exchanged enuresis for pneumonia or the pediatrician is not telling the truth. We must, however, give all credit due for an effort at seeing the light.

Interestingly enough this development in medicine caught also the fancy of the psychiatrist. Already in 1900 there were here and there those voices crying in the wilderness that symptoms were not discrete entities, sorts of uncomfortable pins on which patients found themselves sitting. Our group began to talk about a life process, an unfolding of something which flowered in the psychosis. The psychiatrist began even to say that psychotic manifestations were only the to-be-expected manifestations of disease processes that involved the entire personality.

Here again the same thing has happened that we saw earlier. If the psychiatrist in seeing a life process has leaned heavily on those sonorous sureties of psychopathic personality, inferiority complex and I. Q., no more has he sought their aid than has the pediatrician desperately clung to the weight chart and those other sureties which Dr. Brennemann has so clearly brought to you. He pictures the psychiatrist as that dark villain who furtively poisoned the waters of our need. It is a bit amusing to see his clear recognition of the universal dependence on the concrete, the definite, only to ascribe this to the machinations of a group of persons who, oddly enough, as he names them specifically, are not psychiatricts.

There are still many representatives of the first stage of progress in the field of pediatrics and in the field of psychiatry. Psychiatrists and pediatricians have largely awakened to the newer stage, that of seeing the patient operating as a total or integrated machine. Most specialists looked for the same certainty in this field of new integrations that they had found in the old. Let Dr. Brennemann not fool himself—or you. The search for the concrete, the search for a machine, a standard, a rule of thumb that will relieve us of responsibility and yet give to our pronouncements respectability is of the craving of all mankind. People solidified their accomplishments with medals, sashes and buttons

long before the days of psychiatry. I am no more caught in the glamour of weight charts, I Qs, etc., than is your speaker of a year ago. Our difference is that I see these as the necessities of progress into a new field—as those comforting assurances to the timid.

Just as the development of the laboratory point of view led to an organ pathology, and just as the next step meant the realization that the individual operated as a whole, just so did certain adventuresome physicians suddenly realize that children lived with other people, that this integrated machine had social connotations. Practically all of the medical literature of today, as you know, assumes that the patient is a sort of insulated specimen, not operating with other people. When Dr. William Healy began his brilliant work in Chicago twenty-one years ago, you will realize that psychiatrists looked quite as askance as might have pediatricians. He essentially asked himself but one question: Do stealing, lying and playing hookey have causes? Are these things at all like the rash in some diseases—perfectly normal (if somewhat unesthetic) reactions of the patient toward a more fundamental condition of abnormality? Douglas Thom did not do any more than this when he became interested in faulty habits. It is true that there have blossomed out (under willing hands) a number of rather exotic theories, such as could be used as an explanation for all of the habit difficulties of all children. The latter matter is no more than that which troubles Dr. Brennemann—the need that each of us has in turning to a new field—the need for the concrete, for the mechanical guide.

The development of medicine over the last forty years has been one of orientation to new implications. As the psychiatrist has tried in his child guidance work to carry into the field of conduct only those same approaches that with safety he feels that he can apply to specific pathologic conditions and which with some timidity he applies to the individual as a whole, well may you again expect him to look to the concrete and the certain by way of measurement. I am mystified that you should be disturbed over any present theory as to conduct. It happens that the theories that seem to disturb Dr Bennemann are not those that have been developed by psychiatrists; if he had cared to look on our own formulations, he would have found them altering with a rapidity that should have shown to him that they play no more part in the whole situation than do your weight charts in the growth which you people have made out of an organ pathology into an individual pathology.

The menace of psychiatry is the menace of growth. That group of psychiatrists who have become interested in the relationships of people are, I assure you, considered by most of their colleagues as quite as menacing as they are considered to be by you. Those psychiatrists

who have seen that children are but part of their surroundings and that they must be treated as persons making a social adjustment are just as definitely in advance of their own group as they are of you pediatricians. They are making ridiculous errors and bizarre formulations, as no doubt will the members of other branches of medicine when they choose to see the patient as something other than an isolated and insulated machine.

Now, gentlemen, I personally feel convinced that the presence of other persons is a vital matter to my health and well-being. It is just as ridiculous for you to treat my child without knowing something about me as it is for you to treat the cold extremities of the child without knowledge as to the rest of its economy. These are days when you are talking about pediatrics as ranking with internal medicine. You are no longer to be specialists, you are to treat the whole child! Well, just as surely as you solidify that step will you, too, see the next step in integration, for the child is no mere heap of skin, bones and viscera. In the words of the poet:

> There was a child went forth every day,
> And the first object he looked upon and received with wonder, pity, love, or dread, that object he became,
> And that object became part of him for the day, or a certain part of the day, or for many years, or stretching cycles of years.
>
> * * * * * *
>
> His own parents,
> He that had fathered him, and she that conceived him in her womb, and birthed him,
> They gave this child more of themselves than that,
> They gave him afterward every day—they and of them became part of him.
>
> * * * * * *
>
> Men and women crowding fast in the streets—if they are not flashes and specks, what are they?
> The streets themselves, and the facades of houses, and goods in the windows.
>
> * * * * * *
>
> These became part of that child who went forth every day, and who now goes, and will always go forth every day.

The enuritic child brings with him the mother who must have this to worry over; the frail child carries, too, on his back the overanxiousness of his father's childhood frailty—the tantrums are a settlement with every sort of emotional poverty among the adults at home, if you but chose to see it. I am not telling you anything new, anything of magic or black art. I am simply saying to you what you each already know, namely, that the actions of your sons and daughters are affected by the purposes and aims that come out of your own childhood failures and disappointments and out of your own present family and personal problems. Also I am trying to say that the pediatrician of the future,

just as the psychiatrist of the future, will take these matters into account. Also I am trying to say that what has been called the menace of psychiatry is but the natural craving of persons for certainties as they are stepping out into these new fields.

I have often discussed these matters with pediatricians. They do me the honor of saying that my point of view is not entirely wrong. Indeed such pediatricians as I know rather stoutly and a bit overvigorously tell me that I am only now arriving at a point of view that they have had for many a long year. They have always treated the child as a family problem. I am again minded of Dr. Brennemann's paper: "The pediatrician is intimately familiar with homes in which parents and children are in a normal environment." If that is true, then psychiatry has much to learn from pediatrics. I have tried to discover whether this is true. I went back to my pediatric training in medical school. Our little patients there were totally devoid of human relationships beyond a rather imposing array of persons who were to carry out various of the prescribed regimens for the child. I think again of the problem of enuresis as I met it in medical school. Even in those days the pediatrician was duly shocked at a certain overemphasis on sex that appeared in some of the psychiatric formulations. That came with rather poor grace when enuresis and its treatment gave us students the picture of a bladder and penis in bold relief against a full but rather dimly outlined background consisting of those who were to administer the pediatrician's directions somewhat as though offering sacrifices at the central altar. Were one's eye sufficiently discerning, the child himself could on occasion be observed dimly in some part of the picture. Even today I wonder just how many pediatricians recognize that it is the child himself who wets the bed, rather than the mother, the nurse or the physician.

Finding no answer in these recollections, I began going over my experiences with pediatricians since graduation. There is every sort of pediatrician as there is every sort of psychiatrist. Yet I confess that, in spite of expostulations, I have found pediatricians much more preoccupied with the diseases of children than with children. For instance, I find that pediatricians talk a great deal more with the parents of children than they do with the children themselves. I think I am not unjust in saying that among you I see far too little interest in what the child has to say about his difficulty and far too little of that foolhardy, unquenchable optimism that the child can somehow work out his own salvation if we but strike off the fetters of parental and medical meddlesomeness.

So I did not feel satisfied with these experiences. Then I thought that were the pediatrician's claims true I should find his journals

interesting reading. They are interesting! After going through the recent indexes of your leading journals, I can say only that no psychiatric menace or threat is coming to you through any traitorous disloyalty on the part of your own boards of editors!

Then I had the best idea of all. Perhaps this business of children living as individuals in families is "old stuff" with you. Perhaps it is really such a part of your armamentarium that I should look back ten and twenty years in your journals to find discussions on children as children rather than as some sort of convenient carriers of the pathologic conditions with which I had begun to guess that you are preoccupied. So I went back to your journal indexes of ten and twenty years ago . . .!

With the spread of knowledge, there occurs much that is spurious. Persons run after every loudly shouting new god. Yet I cannot see that this does more than develop responsibilities for the physician, be he psychiatrist, internist, pediatrician or surgeon. If your patients are asking you whether the medical point of view can be applied to the field of conduct, if the parents of your patients are asking you whether their attitudes do affect the health of their children, you are hiding your heads in the sand merely to cavil at those who are trying to formulate guiding principles in this new field. Our ideas of five years ago seem oddly bizarre now, just as the formulations of today will seem grotesque with the passage of another half decade. I hold no brief for the child guidance theories of today. They are efforts at grappling with a new level of integration, and we shall make many trials before getting at anything permanent. I am here to make the plea that you see what we are trying to do and that you come along with us, in full realization that for many years you can only be building for the future, and that for many years you too will turn rather timidly to the certain formulas of sex, inferiority complex, birth trauma, psychopathic personality, I. Q. what not, simply because it is human to turn to a formula as one goes into a new field.

There is one further matter which I wish to discuss. This is represented in some assay of those difficulties which we in child guidance work have found in this new venture. I have every confidence that much that we are doing will be a perfectly comfortable and a necessary part of your armamentarium in the near future. Perhaps if I outline our outstanding errors and problems you will come into the field in a wiser and more efficient way than have we.

1. There is first the question of the body of knowledge involved. Here we who are engaged in child guidance work are at great variance. Essentially we are of two groups. On the one hand are those who believe that we have a new body of knowledge and a certain specific

set of technics. In a general way this group is allied to the psychoanalytic group. The other group feels that we have only a way of looking at things, a point of view, if you please. You will recognize that I ally myself to the latter group. I am not at all convinced that child guidance work involves anything beyond looking at conduct in the same way that one looks on fever, headache or a rash—as merely the natural consequence of some more basic difficulty. If a mother is unusually solicitous as to the supposed ill health of your patient, I am asking no more than that you see that there is just as definite and impelling a reason for this as there is for an acetone breath in certain metabolic disturbances. It is as ridiculous to demand authoritatively that she cease her meddlesome ministrations as it would be to prescribe a mouth wash for the acetone breath. I am not as yet convinced that this involves an enormous addition to your fund of knowledge. Admittedly our medical training will have new orientations; we shall think of our patients as socially operating integrations, and this may introduce certain new technics. In general, however, there will be no more than a different way of looking on the knowledge that we already have. There is nothing startling in the proposition that you give a more willing ear to what the child has to say of his own situation. In a hospital—a good hospital—where I am called to see a number of children I find nicely done record charts, but on them nothing that has been contributed by the child. Whether you term it a menace, a fad or a golden promise, *something* is going to develop to supplement a type of medical procedure that is merely a sublimated form of the veterinarian's mode of approach. Other matters could be used as examples here. May I content myself with Dr. Anna Freud's statement of the psychiatric point of view? It is that of respect for the child, unfailing patience and unquenchable optimism. Here there is nothing which every pediatrician could not cultivate and employ.

I am well aware that our own house is not in order. There are many of my ablest colleagues who would tell you that we have a specific technic which you should learn as you learn some laboratory technic. I am ready to agree that this state of affairs is well calculated to force you to look questioningly at all of us. Personally, I hope that you will see your way clear to putting into your medical school training and into your practice the psychiatric point of view. I also hope that as these matters develop you will find those of us struggling in a new field a little more certain as to the relative values of a technic and a point of view basis for the work.

2. The second matter that is as yet unsettled is that of the relationships of the various disciplines involved in this work. Obviously we are in a field which sincerely calls for all that at least the psychologist, the

educator and the sociologist have to offer. At the present time two courses are open. We can build "teams" in which each of these mighty horses equally firmly attaches himself to the child and then pulls. The psychiatrist in this team combines a saturnine form of prayer with an unparalleled outburst of polysyllabic verbiage in a chance that the horses will pull the child ahead before they pull him apart. The other course open is that the psychiatrist spread himself out over these various fields, impressing himself and his patients with his protean accomplishment. This has its obvious faults, but has the one great advantage of basically serving the fundamental integration of the patient. If I have at all adequately expressed the matter of the psychiatrist's having a point of view, you will recognize my hope that the final adjustment will in some way follow the latter of these two courses. I am convinced that today the psychologist, the educator, the psychiatrist in child guidance work, the psychiatric social worker and the sociologist have, each, a better understanding of the child as a socially operating unit than has the pediatrician. I am also convinced that if your patients come to you with this complaint you are not going to help matters by simply shouting "menace" or "fire." You too must grapple with this problem of striving disciplines—and, for one, I hope that you will find some way out that does not divide the child. Dr. VanIngen sees the teaching of medicine as a matter of recognizing primarily the individual—the individual in relation to his eyes, the individual in relation to his heart, the individual in relation to any other special organ. It seems possible that the time may come when we can think primarily of the child, that we can see him as an integer expressing himself in family, school and neighborhood relationships. The field is now too new for any such formulation, and too full of professional jealousies. It is chaotic in its conflicting claims and in the expostulations of its various interested specialists overcompensating for their insecurity in a new venture. I hope that as you come into the field you will profit enough from our experience to steer clear of this difficulty. Admittedly the physician has not set his house in order in regard to purely physical matters. The position of the specialties seems far from satisfactory as they hungrily look on first the medical curriculum and later the patient.

3. A third matter of equal importance and difficulty continues to trouble us. Perhaps, briefly, it could be stated in terms of expense. If the projects were for research and training in character, as many of them are, it would not seem wise to give a thought to per capita cost. Yet it is undoubtedly true that we do not find any significant diminution in expense in those ventures that have not claimed research or important educational programs. Just how expensive this work can be with

justice has to be decided in the future. As long as its claims that it is preventing adult disaster go without serious challenge, there will be little cavil at its expense no matter how large. Any program that has promise of lightening the load of the adult misfits may well be supported with little quibbling over pennies or even dollars. The child guidance movement has not as yet proved these claims, and perhaps as long as there is uncertainty we are not justified in considering financial matters.

Nevertheless, if for no other reason, this factor of expense stands in the way of any widespread growth. Those adequately trained, the "teams" to be built, the pleas for small intake—all these things seem luxuries to many communities, and to many pediatricians. I suppose that the solution lies somewhere in a dilution of the expert through less expensive mediums and through some sort of generalized popular education. As to the latter, Dr. Brennemann has spoken so sharply and to the point that I scarcely dare attempt a word. May a psychiatrist say, however, that he a bit resents the doctor's remarks as to psychiatrists when his data and quotations are from those who are not psychiatrists? I am interested that Dr. Brennemann so highly speaks of what has been done in the popularizing of medicine in every field except that of psychiatry. I am not at all dismayed at the prospect of popular education, though I believe that we are not as yet ready to undertake it. There is absolutely no reason why, in the course of years, certain data and procedures cannot be given to the public just as you are doing in the purely physical field. This is probably one of the ways of attacking expense, always leaving the specialist for matters more perplexing.

The other method is that of dilution. Here probably enters the psychiatric social worker either as is or as some modification of the present species. Up to the present these workers have been largely conditioned to working with psychiatrists and have largely maintained their medical contacts. In large part their group is better sensitized to the emotional factors involved in human interrelationships than are general physicians and than are most psychiatrists. Unless the medical profession earns its right to lead in this particular field, I see no reason why the psychiatric social workers' group should not ally itself with other interests, psychologic, educational and what not. In fact, it is not unusual to find outstandingly able members of the group already far more closely tied to others than to any medical group. If psychiatry and its miasmic business is a menace, then this is all to the good, a sort of god-sent purification of the medical profession. I have so sincerely hoped that the pediatrician would see the challenge and call of the field of conduct disorders that it had not seemed for the best that the psychiatric social worker lose her medical ties. She may be made a

perfectly comfortable and, I believe, even necessary ally of every pediatrician. With her as such, it seems that a form of dilution can be effected which perhaps represents the most practical present method of meeting the problem of expense.

For our three major problems I have offered no solution. Rather would I have you see that they still present difficulties which are intensely real, difficulties that I bring to you in all frankness in the hope that as you more sincerely enter the field you may know of the traps in which we are caught. Nor have I any more light on the fourth and last of our really unsolved problems.

4. Essentially the fourth problem may be stated thus: Of the things that we find, we are not very sure as to how much belongs to the problem child and how much to the problems of the child. Essentially this is a matter of the extent of clientele. Here we are quite at variance among ourselves, and any such statement that I might make to you would probably gain scant credence from many of my colleagues. Some of us have the utterly absurd view that perhaps one of every three children has been pretty hopelessly tangled in the emotional problems of its parents, and that only fingers of psychiatric deftness can save him. Some of us have an equally absurd view that the problem is scarcely at all specifically individual, that rather are there problems necessarily inherent in all normal growth, and that our task lies in delineating and perhaps ameliorating these. To the second of these grotesqueries I happen to ally myself, and concerning this absurd view should like to speak to you for a few minutes, in full realization that it is your due to hear more definitely some time from some one else some other point of view.

In this matter of clientele, let us go back once more to Dr. Brenneman's paper. Beautifully he pictures the whole clatter, the bang and confusion of modern life. He sees that we cannot go back to the "good old days." He has a solution which takes the child out of all this for awhile. That is just the trouble with pediatricians as the psychiatrist sees them—they think it is too complicated to study the lion in the jungle; so they first safely cage him in a zoo. The psychiatrist has his shortcomings, overstatements and uncertainties, but at least he is trying to study the child as he really is rather than as a glass case specimen.

The fact of the matter is this. We are, as a people, going through great changes in the matter of human relationships. Whether you like it or not, the families which are your clientele are finding themselves face to face with new and profound human and social problems. These matters affect the conduct and health of the patients and serve to make every family part of our clientele, because every family is having to

adjust itself to these changes. You cannot escape these problems and their implications to the child's health by deprecating them, nor can you solve or understand them by setting up a beautiful little experimental station where they do not exist. If you think that the wild theories that modern parents have as to family relationships are dependent on the outpourings of psychiatrists and their hangers-on, you are grievously mistaken. There is today a widespread rebellion against all that is traditional; there is today going on a great decentralization of the family group; there is a rapid dispersion of the family functions; there is a growing economic independence of women, including wives and mothers; there are definite thwarts and social controls and stratifications of the production of workers, high or low. And it is in response to these new challenges that your parents are building new theories, demanding new books, following new gods.

The promise of psychiatry is the promise that if the pediatrician will address himself to these problems he will face a vista of rare challenge. The promise of psychiatry is that children are more interesting than the diseases of children. As surely as I stand here is the type of social problem outlined inherently a part of the problem of every child that you will see tomorrow or have seen today. Those of us who accept this have made our mistakes, and sometimes we think we are pretty well mired. The questions parents ask we cannot answer; the social environment that largely produces these problems we are only beginning to change (as in the school and the court), but the promise is there.

I am not attempting to settle anything in this discussion. In these times of great social change I see for the physician, and particularly for the pediatrician, a real challenge. Personally, I am sorry if he is only afraid of that challenge. Those of us who have gone into the field have made a lot more mistakes than Dr. Brennemann ever thought of cataloging, and if you will come along with us you, too, will make many mistakes; you, too, will timorously cling to the formulas of life. If, on the other hand, you will not come along, if you prefer with Dr. Brennemann to continue to think of the child "without the inhibiting, directing and atmospheric conditions of the parent, or doctor or teacher," then will your patients go elsewhere for real leadership, elsewhere for help with their children, continuing to come to you for help with what are clearly to them the physical *diseases* of their children.

News and Comment

GENERAL

Scientific Exhibit, Milwaukee Session of American Medical Association.—Application blanks are now available for space in the Scientific Exhibit at the Milwaukee Session of the American Medical Association, June 12 to 16, 1933. The final date for filing such applications is Feb. 13, 1933, after which time assignments of space will be made. The Committee on Scientific Exhibit requires that all applicants fill out the regular application form. Persons desiring to receive application blanks should address a request to the Director, Scientific Exhibit, American Medical Association, 535 North Dearborn Street, Chicago.

Bequests.—By the will of the late Edward Guthrie Kennedy the Babies' Hospital of New York receives $5,000.

Postgraduate Courses in Pediatrics.—The Medical Faculty of the University of Vienna is offering its usual postgraduate courses. Those in pediatrics cover fifteen subjects, all by well known teachers.

UNIVERSITY NEWS

Dr. Arthur P. Black, formerly of El Paso, is now associate professor of pediatrics at Peiping University College of Medicine, Peiping, China.

Montgomery Blair, Jr., has been appointed clinical instructor in pediatrics and Loren B. T. Johnson, associate in pediatrics at Columbia University.

Martin J. English, formerly associate professor of pediatrics, has been appointed full professor and head of the department of pediatrics at the Boston University School of Medicine, to succeed the late Orville R. Chadwell.

Herman C. Petterson has been appointed associate professor of pediatrics at the Boston University School of Medicine.

DEATHS

Dr. Orville R. Chadwell, of Boston, died suddenly on Sept. 30, 1932. He was professor of diseases of children at the Boston University Medical School and a member of the American Academy of Pediatrics.

Pediatric Biographies

NICOLAS ANDRY
1658-1742

JOHN RUHRÄH, M.D.
BALTIMORE

The son of a merchant and born at Lyons, Nicolas Andry was educated for the clergy at the Collège des Grassins, where he was made a professor, but after a few years of teaching and acting as tutor he turned his attention to medicine and took the name of Bois Regard. He received his doctor's bonnet at Rheims in 1693, and in 1697 from the Paris Faculty. His thesis was entitled, "An in morborum cura, hilaritas in medico, obedientia in aegro." In 1701 he was named adjoint to the professor of medicine, and the next year he was named censor and became a writer on the *Journal des savans*. He was a facile writer and wrote a score or so of medical treatises and papers besides innumerable criticisms and invectives. His pen was feared by his opponents, of whom he had many.

In 1724 he was made dean of the Faculty of Medicine. He had had more than one encounter with surgeons before this, notably with Petit, and immediately he did all in his power to see that surgeons were shorn of their privileges and that the rights of the Faculty of Medicine were upheld. He maintained that surgery should be taught by the bachelors and doctors of medicine and that candidates should be examined in surgery and made to write a thesis on a surgical subject. This he did not put over, but he managed to have a rule passed that those cutting for stone should do so in the presence of a physician and also that no medical work could be published without the approval of the Faculty of Medicine.

His first book was on worms, a favorite topic in those days. This appeared in Paris in 1700 and was reprinted three times in French; there were also editions in Dutch, German and English. A couple of years later he used the same material in another book, which also went through several editions. He maintained that each part of the body has its special worms which are the cause of disease. The critic Vallisnieri dubbed him "Homo Vermicularis."

He wrote on diet and abstinence from liquors, and on bleeding, purgation and drink. He also wrote numerous papers on diseases of bones.

All his writings save one have long since been forgotten. In 1741, one year before his death, when he was 83 years old, he published "L'orthopédie, ou l'art de prevenir et de corriger dans les enfans les

difformités du corps, etc.," a small work in two volumes which was reprinted in Brussels in 1743; an English edition appeared in London in 1743 and German editions in Berlin in 1743 and 1762. In 1742, "Suite de l'orthopédie" also appeared in Paris.

L'ORTHOPÉDIE
OU
L'ART
DE PREVENIR ET DE CORRIGER
DANS LES ENFANS,
LES DIFFORMITÉS DU CORPS.

LE TOUT PAR DES MOYENS A LA PORTE'E
des Peres & des Meres, & de toutes les
Perſonnes qui ont des Enfans à élever.

PAR M. ANDRY, CONSEILLER DU ROY,
Lecteur & Profeſſeur en Médecine au College Royal,
Docteur-Regent, & ancien Doyen de la Faculté de
Médecine de Paris, &c.

Avec Figures.

TOME PREMIER.

A PARIS, RUE SAINT JACQUES.

Chez { La Veuve ALIX, au-deſſus de la ruë des Noyers, au Griffon.
{ LAMBERT & DURAND, à la Sageſſe, & à Saint Landry.

M. DCC. XLI.

AVEC APPROBATIONS ET PRIVILEGE DU ROY.

Title page of Andry's book.

Andry is said to have been the first to describe infra-orbital neuralgia. He coined the term orthopedics, but his book is more on other topics. Jean André Venel, of Geneva, is generally regarded as the founder of orthopedics as it is understood today, and founded the first orthopedic institute at Orbe, Canton de Vaud, Switzerland, in 1780. Andry's book, however, outlined faulty posture and suggested means of correcting it. The volume is divided into four books, the first of which

deals with "A general description of the external parts of the body." The second is on "Means of preventing and correcting the deformities of the body in children." Book three considers "Deformities of the arms, hands, legs and feet," while book four is on "The means of preventing and correcting the deformities of the head in general." This last book takes up facial deformities, freckles, pimples and the various types of complexion as well as artificial teeth, defects of speech and similar subjects.

An illustration from Andry's book showing the corrective action.

In book two there are directions for standing, sitting and lying and treatment for round shoulders, changes due to rickets, dislocations and fractures. Some of the chapter headings are striking, as for example: "The method of preventing children from pushing out the backside too much," "The body like the back of a spoon" and "Concerning children whose bellies protrude too much." Book three contains a chapter on "The leg or arm shorter for being withered," which is the only mention of a condition that might possibly be construed as poliomyelitis.

If the Leg or Arm is shorter for being withered, the Parents may cure that themselves as we said before by this Method. Rub the Leg or Arm of the child with a bit of scarlet cloth, and renew this Friction several times, but not too roughly, to bring back the animal spirits to the Part. After the Friction anoint the Part with Juniper-Butter a little warm, and then wrap it up in a Linnen cloth. These Frictions and Unctions must be continued several weeks or several months.

Directions for making the juniper butter follow.

Is the following case one of poliomyelitis?

The LEGS become paralytick by a SPRAIN

THE Legs are sometimes strained in such a manner, that although the Misfortune appears to be very slight, yet it renders them paralytick.

A CHILD of six Years of Age, who had stride upon his elder Brother's Shoulders; who used to walk with him in this manner as long as he could every day, in order to divert him. This Diversion at first did the Child no manner of harm, but having repeated it one day as usual, he was seized all at once with a Palsey in both his Legs. His Parents immediately applied such Medicines as they thought most proper, viz., Liniments, Ointments, Essences, hot Mineral Waters, Baths prepared with Ants and the Lees of Claret; and at last, after a great deal of trouble, they got the left Leg cured; but they could not restore the right Leg, which continued paralytick for the space of eight Years, so that he had no manner of use of it. However, they were not discouraged during all that time, but continued to use the same Medicines, which at last had so good an effect that the Patient could walk with the help of a Stick; and thus he continued till the Age of Forty, when he died of an acute Fever, in the Year 1733. But in this Condition he could not walk without describing a Semi-circle with his right Leg, as if it had been an artificial one, though it was abundantly flexible.

THE eminent Dr. *Salzmann,* Physician at *Strasbourgh,* who was a Witness of this, and relates the Case, alleges that the true Cause of this Disease was the violent Tension which the Muscles of the Leg had suffered, while the Child was carried upon his Brother's Shoulders, with his Legs hanging down, one on each Side; and he makes no question, but the first effect of this Strain was to render the Legs paralytick by relaxing the Muscles. To strengthen this Supposition, he brings in the Comparison of a Bow-string, which, by being too much stretched, becomes slack at last, and loses its Force. But it may be asked, how the left Leg came to be cured preferable to the right, though the same Applications were made use of to both? Dr. *Salzmann* offers a Reason for this, which though it is only a Conjecture, yet appears to be pretty natural: it is this, that it is likely that the right Leg, when it was suspended, was more strained than the left (which may very easily be conceived), or that the Vessels of the right Leg had of themselves a greater Disposition to be compressed or obstructed; or perhaps that the spirituous Medicines, which were applied to both the Legs, found a greater Disposition in the Humours of the right Leg, to be dissipated by their too strong Action, than in the left.

The history is taken out of a Latin dissertation by Dr. Salzmann, entitled "Dissertatio medica sistens plurimum pedis musculorum defectum, autore Gotofred Salzmann Doct. Medico, Argentorati, 1734."

Mention is made of some of the orthopedic appliances of the time:

There are several Machines proposed for exercising rickety Children, and making them use such Motions as are capable of setting to rights the Spine and other Parts of the Body; but without having recourse to all those Inventions you can do nothing better for this, than every Morning to throw some Drops of cold Water upon their Face, in the same manner as when you would recover a Person from a fainting Fit. This will oblige them to use such sudden Motions, as will contribute surprisingly to restore the former Shape of those Parts.

The next time you read one of the lurid present-day gland circulars, compare it with the following advice for bronchocele:

Or else, take four Pieces of Cloth of different Colours, green excepted, a Bit of Sponge, and a Dozen of Wood-Lice. The Pieces of Cloth ought each to weigh one Drachm, and the Sponge as much. Burn all together, and when you have reduced them to a Cinder, divide it into four equal Doses, one of which must be taken every Morning fasting, for four days, in a fresh Egg, or a Bit of Bread to disguise it. At the end of the four days begin anew, and continue the same Course as many days longer. 5. You must fill a little Bag of Cloth, with Cork grated down, and tie it about the Child's Neck, and make him wear it Day and Night for some Weeks. 6. Put a Piece of Cork into the Water that the Child drinks, and let it boil for a quarter of an Hour, or thereabouts. The Quantity of the Cork is about four Ounces to four Pints of Water. River-Water is best if it can be had good, but Pump-Water is not to be made use of here.

THIS Cork-Water may be drank either with or without Wine; but at Meals it is best to mix a little Wine with it. Besides, that the Cork may communicate its Virtues to the Water, you must fasten a small Flint to it with a Bit of Thread, so that the Flint sinking to the bottom of the Vessel, may, by means of the Thread, hinder the Cork to swim above, and keep it suspended in the middle.

Pediatrics in Art

CHILD CARE

JOHN RUHRÄH, M.D.
BALTIMORE

Adrian Brouwer (or Brauwer) (about 1608-1640), a pupil of Franz Hals and a "beer friend" of Rubens, painted mostly scenes of drinking and carousing in taverns, scenes with which he was most familiar. He left a painting, "Vaterpflichten," or fatherly care, in which a poor father

"Vaterpflichten" (Fatherly Care), by Adrian Brouwer.

is rendering first aid to his infant—a mute witness that the present-day care of infants by their fathers is not entirely new or unheard of. From the father's expression much can be deduced, especially that the child has some intestinal putrefaction. The painting is in the Dresden Gallery. Brouwer painted a number of pictures of especial medical interest, such as the one entitled "Bitter Medicine" and those illustrating the crude surgery of his day. The photograph is by Königliche Gemälde Galerie, Dresden.

Abstracts from Current Literature

Pathology, Bacteriology and Biochemistry

THE BIOCHEMICAL CHARACTERS OF HUMAN AND ANIMAL STRAINS OF HEMOLYTIC STREPTOCOCCI. PHILIP R. EDWARDS. J. Bact. **23**:259 (March) 1932.

The author summarizes his paper by stating that of 126 strains of hemolytic streptococci, 90 of animal and 36 of human origin, it has been demonstrated that the animal cultures produce a higher acidity in dextrose broth than do the human cultures. It has also been demonstrated that 94 per cent of the animal strains can be clearly differentiated from the human cultures by the fact that they produce acid from sorbite and fail to ferment trehalose. The streptococci of human origin all ferment trehalose and fail to attack sorbite.

STOESSER, Minneapolis.

EFFECT OF ULTRA-VIOLET RAYS ON EPINEPHRINE AND RELATED PRODUCTS (PRELIMINARY REPORT). P. L. EWING, P. BLICKENSDORFER and H. A. MCGUIGAN, J. Pharmacol. & Exper. Therap. **43**:125 (Sept.) 1931.

Exposure of epinephrine to ultraviolet rays produced a decrease in its action on the blood pressure. The action of synephrine tartrate increased, while the base was not affected. Exposure of ephedrine chloride or sulphate to ultraviolet rays caused the drugs to produce a fall instead of a rise in blood pressure, while exposure of the base merely caused a decrease in pressor action. Little change was produced in the action of pseudo-ephedrine, or 1-methyl-ephedrine hydrochloride.

KUGELMASS, New York.

AN EXPERIMENTAL INVESTIGATION OF THE TREATMENT OF TOXAEMIA. G. NORMAN MYERS, J. Pharmacol. & Exper. Therap. **44**:191 (Feb.) 1932.

Guinea-pigs received daily subcutaneous injections of tincture of digitalis for four, six, eight, ten and thirteen days; they were then given lethal doses of diphtheria toxin. The great majority of those that had digitalis for from eight to thirteen days survived, while half of the other groups survived; all the controls died. Daily administration of digitalis begun immediately after the administration of toxin protected against about double lethal doses of toxin and prolonged life against even larger doses.

Strophanthin was less protective than digitalis, but ouabain (crystalline strophanthin) proved inactive. Attempts to protect by single larger doses of digitalis failed. The author takes note of the fact that digitalis is excreted slowly and suggests, tentatively, that digitalis and diphtheria toxin have affinities for the same tissues, and that when digitalis is present in tissue the union of this tissue and toxin is prevented. The author realizes the difficulty of applying these important and instructive results to clinical cases, but suggests that if digitalis is administered early and continuously in the course of toxemias, such as diphtheria and pneumonia, the effect may be most beneficial.

PILCHER, Cleveland.

STUDIES ON THE CORONARY ARTERIES OF THE HUMAN HEART. WILLIAM B. KOUNTZ, J. Pharmacol. & Exper. Therap. **45**:65 (May) 1932.

The author reports studies on the human heart, chiefly from infants and young children shortly after death, on the following subjects: (*a*) coronary outflow in the revived and perfused heart; (*b*) small rings of the coronary arteries, and

(*c*) heart-lung perfusions. Epinephrine, pituitary, ergotoxin, histamine, caffeine, nitrate, morphine, camphor, nicotine and atropine were used. The conclusions are interesting but too long for satisfactory abstraction.

PILCHER, Cleveland.

THE INFLUENCE OF DIET ON CARBON TETRACHLORIDE INTOXICATION IN DOGS. JESSIE T. CUTLER, J. Pharmacol. & Exper. Therap. **45**:209 (June) 1932.

The use of carbon tetrachloride as an anthelmintic had resulted in several deaths, probably from damage to the liver after the manner of chloroform. The author investigated the question in dogs. No diet protected the liver consistently, but certain ones lessened the mortality rate.

Aside from liver damage the important findings were high blood guanidine and hypoglycemia. It is known that calcium antagonizes guanidine. The author, therefore, recommends a diet that should (*a*) not tend to increase guanidine as meat has been shown to do, (*b*) be rich in calcium in order to combat guanidine and (*c*) be rich in carbohydrate in order to relieve hypoglycemia if it develops.

PILCHER, Cleveland.

THE DETERMINATION OF THE SEDIMENTATION TIME OF BLOOD CORPUSCLES. LORENZ FENERSTEIN, Arch. f. Kinderh. **96**:26 (March 4) 1932.

The author describes a method of determining the sedimentation time with a small amount of blood taken from a puncture wound of the finger, the heel or the ear.

LESLIE, Evanston, Ill.

THE BIOLOGIC STANDARDIZATION OF VITAMIN D. J. W. R. EVERSE, Maandschr. v. kindergeneesk. **1**:334 (April) 1932.

In measuring the value of preparations against rickets, in nearly all cases one is obliged provisionally to make use of biologic standardization. The therapeutic as well as the toxic action of the preparations must be investigated. To determine the therapeutic value the healing effect on experimental rickets is recommended. It is advisable to compare several reasonable doses of the preparation to be standardized with such doses of a known standard preparation.

To determine the toxic action of a vitamin D preparation the retarding action on the increase of weight of rats may be taken as a criterion. The limit of the toxic dose was considered as the dose that exactly arrested the increase of weight in a number of rats.

VAN CREVELD, Amsterdam, Netherlands.

Nutrition

THE INFLUENCE OF DIET AND THE ANTERIOR PITUITARY GROWTH HORMONE ON THE GROWTH RATE OF ADOLESCENT RATS. A. HUGHES BRYAN and DAVID W. GAISER, Am. J. Physiol. **99**:379 (Jan.) 1932.

Anterior pituitary growth hormone injected into adolescent male rats definitely accelerated the rate of growth. Other factors influencing the rate of growth were the quality of the diet and the individual growth potential of the particular rat.

NOURSE, Cleveland.

STUDIES IN THE PHYSIOLOGY OF VITAMINS: XVII. THE EFFECT OF THYROID ADMINISTRATION UPON THE ANOREXIA CHARACTERISTIC OF LACK OF UNDIFFERENTIATED VITAMIN B. H. E. HIMWICH, W. GOLDFARB and G. R. COWGILL, Am. J. Physiol. **99**:689 (Feb.) 1932.

The time required for development of the anorexia characteristic of vitamin B deficiency and the amount of food ingested during the period of voluntary food

intake were determined in four dogs under "normal" or basal conditions and during experimental hyperthyroidism. It was found that during hyperthyroidism (1) anorexia appeared in from one half to two thirds of the time required during the control period, and (2) the quantity of food ingested voluntarily per dog was correspondingly increased. The total caloric intakes for the two experimental periods were approximately the same. This suggests that a definite relationship exists between a given amount of vitamin B and the catabolism of a definite quantity of foodstuffs. The four animals successfully maintained their weights by voluntary ingestion of food only when receiving a sufficient amount of vitamin B.

The writers believe that the results of the investigation are of clinical significance. The marked loss of body weight characteristic of hyperthyroidism is well known; in the light of these experiments it is possible that vitamin B deficiency is an etiologic factor. The administration of large amounts of vitamin B to patients with hyperthyroidism is certainly worthy of clinical trial. If one were permitted to generalize, it might be said that vitamin B therapy is indicated in conditions characterized by an increase in the metabolic rate.

NOURSE, Cleveland.

THE TRANSFER OF BICARBONATE BETWEEN THE BLOOD AND TISSUES CAUSED BY ALTERATIONS OF THE CARBON DIOXIDE CONCENTRATION IN THE LUNGS. LOUIS A. SHAW and ANNE C. MESSER, Am. J. Physiol. **100**:122 (March) 1932.

When the alveolar carbon dioxide tension was raised to about 88 mm. by the inhalation of air enriched with carbon dioxide, the carbon dioxide-combining capacity of the blood was lowered 2.1 per cent by volume in dogs, and 4.2 per cent in cats, as a result of the migration of bicarbonate into the tissue fluid. The time required to bring about equilibrium was less than five minutes.

When the alveolar carbon dioxide tension of dogs was lowered to about 8 mm. the carbon dioxide-combining capacity of the blood was increased in some cases by the migration of bicarbonate into the blood, and was diminished in other cases by the migration of bicarbonate out of the blood, the average change being 1.4 per cent by volume of carbon dioxide.

The following hypothesis is offered in explanation of the migration of bicarbonate out of the blood: When the carbon dioxide tension in the lungs is raised, the bicarbonate content of the blood is increased, followed immediately by an increase of the bicarbonate content of the tissue fluids. If the carbon dioxide-combining capacity of the tissue fluids is exactly equal to that of the blood, the bicarbonate level in the two systems of fluid remains equal. Under these conditions no transfer of bicarbonate between the blood and the tissue fluids takes place. On the other hand, if the carbon dioxide-combining capacity of the blood is greater than that of the tissue fluids, an increase in the carbon dioxide tension of the lungs causes the formation of more bicarbonate in the blood than in the tissue fluids, and the bicarbonate level in the blood rises above the level attained in the tissue fluids. Under these conditions bicarbonate moves out of the blood into the tissue fluids until equilibrium is again established.

NOURSE, Cleveland.

THE DESTRUCTION OF VITAMIN A BY ULTRA-VIOLET RADIATIONS. ROBERT J. NORRIS, Bull. Basic Sc. Research **3**:89 (May) 1931.

Biologic and colorimetric methods of assay of irradiated cod liver oil show a wide discrepancy in the estimated vitamin A content. Irradiated oils practically inactive in feeding experiments may show from 50 to 75 per cent of the original vitamin activity as judged by the color reaction. By biologic tests, a definite induction period of as much as one hour has been followed by rapid destruction

in an equal subsequent period. Under the conditions of these experiments, practically complete inactivation occurs after eight hours of full ultraviolet irradiation, as judged by feeding experiments. The destruction of the chromogenic substance has been shown to follow a bimolecular reaction, and no induction period has been demonstrated for it. The results indicate that the chromogenic substance, while closely following vitamin A, is not the vitamin itself; hence the colorimetric measurement of this factor cannot be relied on under all conditions.

KUGELMASS, New York.

CALCIUM AND PHOSPHORUS STUDIES: IV. THE RELATION OF CALCIUM AND PHOSPHORUS OF THE DIET TO THE TOXICITY OF VIOSTEROL. DAVID H. SHELLING and DOROTHY E. ASHER, Bull. Johns Hopkins Hosp. **50**:318 (May) 1932.

This paper presents a study of the relation of varying amounts of calcium and phosphorus in the diet to the toxicity of irradiated ergosterol in the rat.

The diets were of the following varieties: (*a*) low calcium and optimal phosphorus; (*b*) low calcium and high phosphorus; (*c*) stock diet, optimal calcium and phosphorus; (*d*) minimal calcium and high phosphorus; (*e*) high calcium and low phosphorus, rachitogenic; (*f*) high calcium and optimal phosphorus; (*g*) high calcium and high phosphorus; (*h*) calcium-free, and (*i*) calcium-free and phosphorus-free.

The dosage of irradiated ergosterol, given in terms of cod liver oil potency, varied from 1 per cent of the diet to twenty thousand times that amount. In terms of overdosage, the amounts of the viosterol varied from four to eighty thousand times the amount of the diet, since 0.25 per cent of cod liver oil in the diet is the minimal curative dose.

The effect of these procedures on the serum calcium and inorganic phosphorus, growth and weight, reproduction, offspring, soft tissues and bones was observed.

The authors summarize their results as follows: 1. The calcium and phosphorus content of the diet is a determining factor in viosterol toxicity in rats. (*a*) Optimal calcium-high phosphorus diets are the most predisposing to the injurious effects of viosterol, and high calcium-low phosphorus and low calcium-optimal phosphorus diets are the least effective. (*b*) On the stock diet in which the calcium and phosphorus contents are optimal, dosages of irradiated ergosterol from several hundred to a thousand times the therapeutic dose produce no detectable injurious effects when fed for long periods. On this diet, the therapeutic dose is quite remote from the toxic level. 2. Metastatic calcification is not the sole injurious effect of irradiated ergosterol, for necrotic, degenerative and inflammatory changes without calcification occur in the soft tissues when large doses are used. 3. Small or moderate doses of irradiated ergosterol cause deposition of calcium and phosphorus in the bones, while large doses may cause resorption of lime salts from the bones. 4. The arterial calcification produced by irradiated ergosterol is of a specific type and is limited chiefly to the media, as in Monckenberg's sclerosis, rather than to the intima, as in arteriosclerosis. 5. Irradiated ergosterol is capable of raising the serum calcium to hypercalcemic levels when calcium is entirely absent from the diet and of elevating it from hypocalcemic levels produced by high phosphorus feeding.

LYTTLE, New York.

CALCIUM AND PHOSPHORUS STUDIES: V. THE COMPARATIVE EFFECTIVENESS OF VIOSTEROL AND COD LIVER OIL IN PROTECTING THE BODY AGAINST A CALCIUM DEFICIENCY IN THE DIET. DAVID H. SHELLING and DOROTHY E. ASHER, Bull. Johns Hopkins Hosp. **50**:344 (May) 1932.

The basal diet was lacking in vitamin D and low in calcium, but adequate in all other respects. Different diets gave a range of deficiency in calcium and were fortified with comparable amounts of cod liver oil and viosterol.

The effect on growth, reproduction, serum calcium and inorganic phosphorus, skeleton, teeth and hair was observed. The tendency for pica and coprophagy was noted.

The authors conclude that there is no demonstrable difference in the physiologic effects of cod liver oil and viosterol in sparing body calcium in rats fed diets adequate in all respects except for a paucity in calcium, and that growth and reproduction are improved with increase in calcium and vitamin D of the diets.

LYTTLE, New York.

IRRADIATED MILK IN THE TREATMENT OF RICKETS (A RÉSUMÉ). E. B. HARDESTY, M. J. & Rec. **135**:289 (March 16) 1932.

Cod liver oil has long been considered an antirachitic, although the continued prevalence of rickets plainly indicates the ineffectiveness of the treatment, which is undoubtedly due to lack of cooperation in those caring for the children, as well as the fat intolerance of the patients themselves. The difficulties that arise from the use of irradiated ergosterol, such as overdose hypercalcemia and similar conditions, seem to preclude its being of universal benefit in the prevention and cure of rickets. Although sunlight is of recognized value in the prevention of rickets, it will not suffice to construct a calcareous bone in the absence of the elements that constitute its organic ingredients. The clinical value of irradiated milk will go far in establishing this method of treatment (preventive and curative) of rickets. In order that milk shall be effectively antirachitic in potency, certain standards of radiation technic must be observed, as shown by the pioneer work done by the Research Laboratories of the Dry Milk Company at Bainbridge, N. Y. Dr. A. F. Hess reported results from the use of 1.2 per cent butter-fat milk, which showed that this milk is definitely antirachitic in power.

WILLIAMSON, New Orleans.

CHOLESTEROLEMIA AND ITS RELATION TO THE SERUM ALBUMIN IN NUTRITIONAL DISORDERS OF INFANCY. P. NOBÉCOURT, A. COMNINOS and P. DUCAS, Arch. de méd. d. enf. **35**:249 (May) 1932.

Investigations on the blood of the new-born have stressed particularly the metabolism of the chlorides and nitrogen bodies without giving more than passing notice to cholesterol.

In the course of prolonged studies in cases of chronic digestive disturbances, advanced to an extreme state of cachexia, the authors had occasion to estimate through proper quantitative analyses the mean level of this complex body; the method employed was that of Gregaut the chemist. Acute nutritional disturbances and disorders complicated by syphilis or tuberculosis were eliminated in these examinations. The normal content of cholesterol as estimated by Lesné, Zizine and Sylvestre was accepted as a standard; this quantity varies from 0.8 Gm. per liter of serum at 2 months to 1.2 Gm. between this age and 18 months. The percentage of serum albumin in these cases was determined by the refractometric index of Abbe, which seems more practical in pediatric investigations. Reiss and Jaccottet have shown that the index varies little in normal infants; it demonstrates the mean level of the albumin to range between 56 and 66 Gm. per thousand cubic centimeters in babies under 6 months; in older infants the content rises to about 75 Gm. Most of the biochemists cited found an increase of albumin in diarrheal disturbances; in the authors' cases the content varied from 76 to 95 Gm. There was no parallelism between the albumin content and the amount of cholesterol. The variations of the latter could not be explained by the dilution or the concentration of the blood.

In rachitic infants, hypercholesterolemia is commonly found, while in bronchopneumonia, angina and certain other infections the quantity is reduced.

AMESSE, Denver.

THE ETIOLOGY AND PATHOLOGY OF GENERAL ATROPHY. VICTOR VILADRICH, Med. de los niños **32**:340 (Nov.) 1931.

The various theories of the causes of athrepsia are reviewed, such as insufficient food, inability to secure the food because of feeble sucking power, esophageal stenosis, dysphagia, adenoid vegetations, deprivation of breast milk, cyclic vomiting, congenital debility and infections of the bowel. Under the chemical theory are described the difficulties of digestion and of assimilation of cow's milk leading to alimentary intoxication of Finkelstein.

DWYER, Kansas City, Mo.

INFANTILE SCURVY. CÉSAR PÉREZ VICTORIA, Med. de los niños **33**:10 (Jan.) 1932.

Scurvy was early described by Moller as acute rickets, and it was not until the later work of Forster and of Barlow that the pathologic changes were studied and the true character of the disease became known. These investigators found alterations in the blood with periosteal and gingival suffusions. Today the periosteal changes are more frequently observed than are the hemorrhages into the gums. The disease is most common from the fifth to the eighth month of life according to some observers. It is frequently erroneously diagnosed as rheumatism, erysipelas or osteomyelitis. The disease is the result of a deficiency in the water-soluble vitamin C. This substance is present in abundance in green vegetables and fruits. It is especially sensitive to contact with the air and oxygen, and above all alkalinization tends to destroy it.

Autopsies have demonstrated hemorrhages in the dura mater of sufficient extent to produce convulsions, and diagnoses have been made during life by means of spinal puncture.

DWYER, Kansas City, Mo.

THE EFFECT OF HEAT IN THE ETIOLOGY OF DIGESTIVE DISTURBANCES IN INFANTS. S. E. BURGHI, Rev. franç. de pédiat. **7**:766 (Dec.) 1931.

The author reviews the subject of cholera infantum and concludes that an increased temperature is the primary cause of this condition. Clinically it is known that most cases occur in the summer months following a spell of warm weather, and that no causative organisms are ever found. When excess water is needed, the body uses so much to overcome the accompanying dehydration that a deprivation of two thirds of the necessary water causes a diminution of the alkaline reserve, which is the beginning of the condition.

SANFORD, Chicago.

A CASE OF SEVERE RACHITIS TARDA. V. ČECH, Časop. lék. česk. **69**:864 (June 6) 1930.

The author reports the case of a boy of 18 years with marked kyphoscoliosis and lordosis, marked deformity in the lower extremities and only slight deviation of the upper extremities. The differential diagnosis includes rickets, osteomalacia, idiopathic osteopsathyrosis of Lobstein, osteogenesis imperfecta tarda, fetal chondrodystrophy and osteopathy of starvation. There was a pathologic fracture of the tibia at 5 years, of the femur at 12, and progressive deformity, so that since 15 he has been unable to walk. The blood calcium was 10.2 mg., and the basal metabolism was plus 7 per cent. Photographs and roentgenologic findings are given.

STULIK, Chicago.

DWARFISM IN HUMAN BEINGS. A. J. P. BROEK, Časop. lék. česk. **69**:962 (June 27) 1930.

The author divides dwarfism into the groups of pathologic, primordial and familial, with a subdivision of the first group into pathologic dwarfism in the strict sense of the word, infantilism and teratologic dwarfism. A general review on dwarfism and nanism is given.

STULIK, Chicago.

CAROTIN AND VITAMIN A AND THE PRACTICAL SIGNIFICANCE OF THEIR MUTUAL PHYSIOLOGIC RELATIONS. P. G. F. VERMAST, Maandschr. v. kindergeneesk. **1**:258 (Feb.) 1932.

In this article a short survey of the present knowledge of the carotin-vitamin A problem is given.

VAN CREVELD, Amsterdam, Netherlands.

THE DIRECT DIAGNOSIS OF RICKETS AS AN INDICATION FOR THERAPY. E. J. M. BELINFANTE, Maandschr. v. kindergeneesk. **1**:293 (March) 1932.

It is often difficult to say directly whether one has to do with active rickets. This knowledge may, however, have great value for therapy. The author studied the question extensively in fifty-nine children varying in age from 3 months to 3 years. Direct treatment in her opinion is indicated in severe cases of rickets occurring in older children and in young children when distinct symptoms of softening of the bones are present.

VAN CREVELD, Amsterdam, Netherlands.

Prenatal Conditions

COMBINED CONGENITAL EXSTROPHY OF THE FEMALE URINARY BLADDER AND CLOACA. GRAHAM KERNUSIN, Arch. Path. **13**:926 (June) 1932.

The author reports a case of combined congenital exstrophy of the female urinary bladder and cloaca, observed in a full-term child that lived four days after birth. There were no other abnormalities except a left equinovarus. The umbilical cord had a long base through which loops of bowel were visible. Below this from a defect of the anterior abdominal wall protruded the mucosal surface of an evaginated segment of bowel. Urine and feces passed onto that surface. Examination made at autopsy showed a soft red mass into which were openings from the ileum, a blind segment of bowel and a small appendage, apparently the appendix; laterally were the paired openings of cone-shaped appendages (the fallopian tubes) and, lateral to these, the openings of the ureters. The colon was absent. Various explanations of the phenomena are discussed.

LESLIE, Evanston, Ill.

MECONIUM PERITONITIS. W. S. BOIKAN, Arch. Path. **14**:50 (July) 1932.

A case is reported of meconium peritonitis due to spontaneous perforation of a Meckel's diverticulum estimated as having occurred near the end of the fourth month of intra-uterine life. At the site of the perforation there was excessive development of lymphoid tissue containing very deep glands of Lieberkühn and focal disappearance of the muscular layer.

LEMASTER, Evanston, Ill.

THE CARE OF PREMATURE INFANTS. MARSH W. POOLE AND THOMAS B. COOLEY, J. Pediat. **1**:16 (July) 1932.

Details in the management and feeding of premature infants in the Children's Hospital of Michigan during 1930 and 1931 are thoroughly discussed. A special cubicle for premature infants is used. The temperature is kept constantly at 80 F. by steam heat, and a humidifier is operated to keep the relative humidity at from 55 to 60 per cent. The incubators consist of infant cots, heated by electric light bulbs and covered with blankets and sheets so as to leave an opening directly over the infant's head. Baths of warm oil are given daily, while baths with soap are administered only once a week. Strict isolation of the cubicle is maintained. Nose and throat cultures in cases of respiratory infections were found almost invariably to yield Micrococcus catarrhalis or streptococci and were found to be of great value in diagnosis. Brewer's yeast and prophylactic vaccine therapy produced no increase in resistance to respiratory infections. Cod

liver oil is added to the milk formulas from the day of admittance, and ultraviolet irradiation is given twice weekly as a routine. No evidence of active rickets has been seen except in those infants who had severe infections, and in these brewer's yeast seemed to aid calcification. Saccharated ferrous carbonate produced good results in mild secondary anemia. Injections of blood are given for the severe anemias due to infection. The initial loss in weight is combated by giving 5 per cent dextrose immediately on admittance, starting the regular feeding schedule within six hours and giving saline hypodermoclyses when the infants are unable to take fluids by mouth. Breast milk containing 2 per cent calcium caseinate is fed to infants weighing less than 1,800 Gm., and after satisfactory gain is established an evaporated milk formula is used. Most of the infants were found to gain well on from 120 to 140 calories per kilogram. The emptying time of the stomach and the hydrogen ion concentration of the gastric juice were found to be about the same for the infants receiving breast milk as for those receiving unacidified evaporated milk. The follow-up service designed to teach the mothers and to supervise the care of the infants after going home has proved satisfactory in reducing the mortality and morbidity. The premature infants after one year compared favorably with full term infants in development except for later dentition.

LEMASTER, Evanston, Ill.

AN AID IN THE DIAGNOSIS OF A CERTAIN TYPE OF CONGENITAL ESOPHAGEAL STENOSIS. M. L. REID, J. Pediat. **1**:87 (July) 1932.

A case of complete esophageal stenosis with communication between the trachea and the lower esophageal segment is described. The roentgenogram showed the stomach to be distended with gas. Feeding through the gastrostomy opening caused regurgitation of food into the lungs and apparently produced the pneumonia which was fatal.

The author suggests that in congenital esophageal stenosis, if the roentgenogram shows the stomach filled with gas, a communication between the trachea and the lower esophageal segment should be suspected and jejunostomy is preferable to gastrostomy. He also suggests injection of iodized poppy seed oil into the trachea as a means of confirming the diagnosis of this particular anomaly.

LEMASTER, Evanston, Ill.

CONGENITAL HEART DISEASE WITH SPECIAL REFERENCE TO ITS ETIOLOGY. SAMUEL ADAMS COHEN, M. Clin. North America **15**:1295 (March) 1932.

Cohen reviews the modern classification of congenital cardiac defects and reports two cases as a basis for discussion of the etiology, diagnosis and prognosis. Concerning etiology, the factors of fetal endocarditis and the persistence of conditions normal in the fetal circulation have long held the attention of clinicians. A third factor, diminished fertility on the part of the female and possibly a variation in virility on the part of the male element, has been brought forward as a cause of fetal abnormalities. Should further studies confirm these observations, the clinician may find it possible, by control of these factors, in some measure to prevent the development of certain congenital defects.

SMITH, Ogden, Utah.

CONGENITAL OBSTRUCTION OF THE DUODENUM IN CHILDREN. WILLIAM E. LADD, New England J. Med. **206**:277 (Feb. 11) 1932.

These obstructions may be grouped into two classes: the intrinsic or intramural type, in which the obstruction is caused by septums within the lumen of the bowel, and the extrinsic, or extramural type, in which the obstruction is caused by pressure on the outside of the bowel. In the author's experience, the extrinsic type is dependent on an incomplete rotation of the bowels.

In patients with complete atresia, vomiting begins shortly after birth. It is explosive in character, resembling that of pyloric stenosis, but differing in its time of onset. The content of the vomitus in duodenal obstruction contains bile, whereas that in pyloric stenosis does not. On physical examination, visible gastric and occasionally duodenal peristalsis is to be seen. Confirmatory evidence of the obstruction may be obtained by means of roentgenograms with or without a barium meal. In cases of complete atresia, there being no gas below the point of obstruction, a roentgenogram taken without the ingestion of barium gives conclusive evidence of the point of obstruction. In cases of partial obstruction there is gas throughout the intestines, so that a roentgenogram without the ingestion of barium is of no value. Patients with complete atresia who are not operated on die of inanition, usually within ten days after birth, although there are a few cases in the literature of patients who lived for an extraordinary length of time. Patients with incomplete obstruction may present symptoms soon after birth and may live for a considerable period with little disturbance. In the case of such patients the duodenum enlarges to a much greater extent than in patients with complete atresia. Vomiting is intermittent in character, patients going weeks or even months without symptoms. The infants are usually poorly developed and nourished, and their weight is usually considerably below normal for their age.

A careful review of the literature showed but ten cases of successful treatment. In 1916, Ernst reported the case of an infant of 11 days with atresia of the duodenum successfully treated by anterior duodeno-entero-anastomosis. The author discusses some of the important points in the operative technic. Though shocking, he feels that the only way to reduce the volvulus is by delivering the whole small bowel and by untwisting it.

"Because of the frequency of postmortem reports of these cases and the infrequency of these conditions in adult life, one infers that the mortality is high without surgical intervention. The fact that we have had ten of these cases in a comparatively short period of time, leads one to believe that we have undoubtedly overlooked these cases in the past and that they are more common than has been supposed. That seven of these ten patients have been apparently cured by operation emphasizes the importance of recognizing the condition and giving such patients the benefit of surgery. In our experience, the operations which have proved successful are posterior gastrojejunostomy, posterior duodenojejunostomy, reduction of mid-gut volvulus and freeing of cecal attachments."

The author gives detailed reports of the ten cases. GENGENBACH, Denver.

CONGENITAL ABSENCE OF PART OF THE ABDOMINAL WALL. H. A. GAMBLE, South. M. J. **25**:771 (July) 1932.

The author reports this condition in a white male child born at term and weighing 5 pounds (2.3 Kg.). A plastic operation was performed immediately after birth, repairing the defect. A modified Mayo operation for umbilical hernia was employed.

The author points out that congenital defects involving the absence of fascia and musculature are comparatively rare. Only about eighteen other cases have been reported in the literature.

The condition in most of the cases is inoperable, but when it is operable it should be taken care of immediately. SCHLUTZ, Chicago.

ABRACHIATISM; REPORT OF TWO CASES. J. HOLDEN ROBBINS and LAWRENCE V. LITTIG, Wisconsin M. J. **31**:323 (May) 1932.

In both patients the upper extremity distal to the scapula was completely absent. One patient died at the age of 1 month. Anatomic dissection showed no other abnormality. The brachial plexus was normal in origin, and the muscles

also ended in a fibrous mass at the point of amputation. Blood vessels terminated in the same way. A cartilaginous mass protruding from the lateral angle of the scapula embodied both the glenoid cavity and the coracoid process.

In the second child, who is healthy at 2 years of age, both upper extremities distal to the scapula are absent, and there is talipes equinovarus of the right foot. No other abnormalities were noted, but there is a scoliosis believed to be due to a resistant case of rickets. A distant relative of the child had congenital absence of both legs from the knees downward. The authors believe that congenital anatomic deformities occur as the result of mutation of the genes of the chromosomes.

JANNEY, Milwaukee.

INCOMPLETE DEVELOPMENT OF STRIATED MUSCLE FIBER AS A CAUSE OF CERTAIN DEFORMITIES OF THE EXTREMITIES. D. STEWART MIDDLETON, Edinburgh M. J. **39**:389 (June) 1932.

In a short preliminary note the author offers proof that defective growth of striated muscle may be responsible for such deformities as associated bilateral clubfoot and clubhand (without bony malformation) known in human beings, and also in sheep, as "arthrogryposis multiplex congenita." On dissection in cases of congenital high scapula a shortened muscular or fibrous band uniting the scapula to the vertebral column or to the skull is also found. Another instance was disclosed in a case of apparent absence of the muscles of the neck; on dissection, the tissue of the sternocleidomastoid muscle was found to consist of embryonic myoblast cells. The failure of growth of the muscles of the calf in a case of congenital angling of the tibia with fixed pes equinus was found to be the cause of the shortening in another instance. Certain striated muscles, therefore, may fail to undergo their complete development, thereby failing to become elastic or long enough for the other structures of the extremity. Abiotrophic muscles should be regarded as the etiologic factor in producing such deformities.

NEFF, Kansas City, Mo.

INFANTILISM WITH LOCAL OVERGROWTH. A. G. MAITLAND-JONES, Proc. Roy. Soc. Med. **25**:416 (Feb.) 1932.

A case is reported in a girl of 6½ years which was reported as a case of progeria in 1928. In this paper it is reported as a case of infantilism, the patient weighing 14 pounds and 12½ ounces (6.7 Kg.). Her height was 33 inches (83 cm.). The nose and superior maxillae appeared overdeveloped, and the hair was thick and long, reaching to the waist. The sella turcica was normal in size, but the whole skull was very small.

WILLIAMSON, New Orleans.

COARCTATION OF THE AORTA. A. C. HAMPSON, Proc. Roy. Soc. Med. **25**:420 (Feb.) 1932.

A case of coarctation of the aorta was reported in a boy of 12 years.

WILLIAMSON, New Orleans.

RIGHT HEMIHYPERTROPHY AND PUBERTAS PRAECOX. JOAN HARWOOD, Proc. Roy. Soc. Med. **25**:951 (May) 1932.

A case of right hemihypertrophy and pubertas praecox was reported in a boy 6½ years of age. At birth the mother thought he looked "one-sided" and a photograph taken at 2 months showed a marked difference between the right and left arms and legs. About eighteen months before the author saw the child the parents noticed that the genitalia were growing larger on the right side. The mental development and habits were good. A diagram of the skull showed no other abnormality than that the skull was somewhat large for a child of his age.

Subsequent examination revealed a palpable tumor in the right loin suggestive of a large kidney. The question then arose as to whether this was an enlarged kidney or a suprarenal tumor.

WILLIAMSON, New Orleans.

CONGENITAL ESOPHAGEAL STRICTURE TREATED BY DILATATION. GERTRUDE HERZFELD, Tr. Med.-Chir. Soc., Edinburgh, 1932, p. 15; in Edinburgh M. J., February, 1932.

A small boy, about 3 years of age, examined after the administration of a barium meal showed an esophageal dilatation ending in a constriction opposite the seventh thoracic vertebra. The author believes that the child has a shortened esophagus and a thoracic stomach, an obstruction similar to cardiospasm. The passage of a no. 10 gum elastic bougie on two occasions permitted the child thereafter to swallow soft solids without vomiting. Findlay has reported seven such cases in which the obstruction ended at this same site.

NEFF, Kansas City, Mo.

DYSCHONDROPLASIA: REPORT OF A CASE. J. DE BARRIN, Rev. d'orthop. **19**:222 (May) 1932.

The author reports a case of dyschondroplasia in a child of 17 months. The report is complete with roentgenograms. There was no history in the family of any similar deformity; the child walked alone but with difficulty, tired easily and fell frequently. The left leg was shorter than the right and was increasingly so. The patient's general health was excellent. Roentgenograms showed hypertrophy of the cortex of the diaphysis, with lessened density, and separation by a denser layer from the normal appearing shaft. The left arm was also involved.

The clinical picture was that of a generally healthy child, of slightly subnormal mentality and exaggerated adipose tissue; the thyroid was normal in size and shape, and the Wassermann reaction, negative. There was no pain on pressure.

Ollier states that dyschondroplasia is always unilateral. Müller has demonstrated by roentgenograms that bilateral lesions occur, and Molin has reported one case of bilateral involvement. The present case is unilateral, both upper and lower limbs on the left side being involved.

RYAN, Vancouver, B. C.

A CASE OF SITUS INVERSUS VISCERUM TOTALIS. AGUSTIN FERNANDEZ LAGOS, Rev. chilena de pediat. **3**:113 (March) 1932.

The author reports a case of situs inversus viscerum totalis in a 2 year old child who died of bronchopneumonia following measles. Autopsy revealed a complete inversion and transposition of the heart and its chambers, the lungs, the thoracic aorta and the esophagus as well as a complete transposition and inversion of all the abdominal viscera.

SCHLUTZ, Chicago.

THREE CASES OF CONGENITAL HYPERTROPHY IN CHILDHOOD. B. DRAGISIE, Arch. f. Kinderh. **96**:165 (May 6) 1932.

Of the three cases of congenital hypertrophy reported by the author, one consisted of a complete hemihypertrophy, with the exception of the head; the second, of hypertrophy of the lower extremity only, and the third, of hypertrophy of one half of the head. All tissues took part in the hypertrophy, including the skeleton. In the third case, the teeth, tonsil and the gums were definitely larger on the involved side. Two of the cases showed pigmented nevi. Various theories as to the origin of this condition are discussed. These are the embryonal, mechanical, neurotropic, the blood vessel and the endocrine theories.

LESLIE, Evanston, Ill.

CARBON DIOXIDE IN THE RESPIRATORY DISTURBANCES OF PREMATURE AND NEW-BORN INFANTS. PEIPER, ALBRECHT and OTTO CAMMANN, Monatschr. f. Kinderh. **53**:323, 1932.

In order to test the hypothesis of Henderson, the writers used mixtures of ordinary air, oxygen and carbon dioxide—in most cases oxygen mixed with 5 per cent carbon dioxide. They are not at all convinced that the addition of carbon dioxide to oxygen is of particular value; undiluted carbon dioxide is certainly inferior to stimulants such as lobeline or epinephrine.

GERSTLEY, Chicago.

PROBLEMS OF PREMATURITY. JOHANNES SCHOEDEL, Monatschr. f. Kinderh. **53**: 349, 1932.

The writer reviews the problems connected with prematurity from the point of view of his special experience in Chemnitz. Of one million births annually in Germany, about 10 per cent are premature. Of course this percentage varies in different localities. The prognosis is relatively good for children over 1,500 Gm. Under that weight, children require the combined efforts of the obstetrician and pediatrician.

The percentage of premature births has diminished somewhat in the last decade in Germany, due unquestionably to the better nutrition of the women. The constitutionally weak mother usually carries the pregnancy through the first months but later is inclined to premature labor. Syphilis must give way to multiple pregnancies and to abnormal positions in the uterus as a cause of prematurity.

In feeding premature infants the writer believes that the ordinary relatively large volume of food may interfere with the heart's action by a pressure through the diaphragm. To avoid this, following meals he has the children placed in a more upright position, and believes that he has reduced the number of attacks of asphyxia.

GERSTLEY, Chicago.

AN UNUSUAL MALFORMATION OF THE SPINAL COLUMN. W. MÜLLER, München. med. Wchnschr. **79**:356 (Feb. 26) 1932.

Müller reports the absence of the posterior spinous process of the second lumbar vertebra in a man, aged 38. This malformation has not been described before. The inferior articular processes of the second lumbar vertebra are also absent, but the superior articular processes of the third lumbar vertebra are present (there is an illustrative roentgenogram). The description of such a congenital malformation is important, not only because of its rarity, but because it demonstrates that the spinal column can be maintained in its normal position when the bony articulations between two of the vertebrae are absent. In this case the intervertebral disk maintained the articulation between the second and third lumbar vertebrae.

BRAHDY, Mount Vernon, N. Y.

Diseases of the New-Born

TRANSECTION OF THE SPINAL CORD IN THE NEW-BORN. R. K. BYERS, Arch. Neurol. & Psychiat. **27**:585 (March) 1932.

The authors describe a case of transverse myelitis of the lower cervical cord due to obstetric trauma in an infant who lived four months. This was long enough to show a degeneration of the cord. The authors described the extensive and complex reflex activities that were carried on through the isolated lower segment of the cord as compared with those of the normal infant.

BEVERLY, Chicago.

BREECH DELIVERY. J. T. SHERMAN, Bull. Lying-In Hosp. **13**:344 (Feb.) 1932.

Breech presentations occur in from 3 to 4 per cent of deliveries. The fetal mortality ranges from 9 to 20 per cent. The author reports on forty-two breech deliveries with a fetal mortality of 7.5 per cent. Seventy-five per cent of the babies die of injury to the fetus rather than of asphyxia, and for that reason the policy of "hands off as long as labor is advancing" is advocated by the author. The tradition of an eight minute period before asphyxia occurs in breech delivery need not be adhered to. The risk of intervention is greater than that of reasonable delay.

KAISER, Rochester, N. Y.

ERYTHROBLASTOSIS OF THE NEW-BORN. STEWART H. CLIFFORD and ARTHUR T. HERTIG, New England J. Med. **207**:105 (July 21) 1932.

This pathologic picture consists of a continuation of or a reversion to the embryonic level of blood formation with large numbers of nucleated red cells in the circulating blood and active hematopoiesis in the liver, spleen, pancreas, kidneys, suprarenals, thymus, pituitary gland and lymph nodes as well as in the bone marrow.

The authors review the literature and report a study of seven cases of erythroblastosis of the new-born (two of the congenital hydrops type and five of the icterus gravis variety) seen at the Boston Lying-In Hospital during the past nine months. Five of the seven patients died and showed the pathologic picture of erythroblastosis at postmortem examination.

Congenital hydrops is of rare occurrence, and the incidence has been reported as 1 in from 2,000 to 3,000 births. The authors' rate of incidence was 1 in 1,200 births.

Icterus gravis has also been considered as of rare occurrence, but actual figures are not available. On the basis of the experience at the Boston Lying-In Hospital erythroblastosis is far from a rare disease, as there were seen seven proved cases in the past nine months; in this period 2,400 babies were born, resulting in an incidence of erythroblastosis of 1 in 340.

GENGENBACH, Denver.

CAUSES OF DEATH IN THE NEW-BORN. A. COUVELAIRE and M. LACOMME, Nourrisson **20**:137 (May) 1932.

The highest death rate was found in babies weighing under 2,500 Gm.; the smaller the weight, the higher the mortality which reached 76 per cent in infants weighing less than 1,500 Gm. With healthy parents the most common causes of prematurity are: twins, uterine hemorrhage, premature rupture of membranes, and endometritis.

The diseases responsible for interruptions of pregnancy in the order of their frequency are syphilis, tuberculosis, nephritis including eclampsia and acute and chronic infections. The mortality in malformed fetuses is high, and obstetric trauma takes its toll. The percentage of prematurity is higher with mothers who find it necessary to work during pregnancy.

MCCLELLAND, Cleveland.

CUTANEOUS INDURATION OF THE NEW-BORN WITH HISTOLOGIC STUDY. WALTER PIAGGIO GARZÓN, Med. de los niños **32**:299 (Oct.) 1931.

An infant, aged 16 days, presented numerous subcutaneous nodules (eighteen) on the back, arms, neck and right leg. These indurations diminished in size until they totally disappeared. The father had subcutaneous nodules that resembled lipomas. Biopsy of the father's tumors revealed large masses of adipose tissue, with multinucleated giant cells, undergoing chemical changes, and saponification of the subcutaneous fatty tumors. The condition is compared with scleroderma and with sclerema.

DWYER, Kansas City, Mo.

MECONIUM PERITONITIS BY SPONTANEOUS PERFORATION OF THE INTESTINE. MARTIN JACHENS, Monatschr. f. Kinderh. **53**:188, 1932.

This is the report of three cases, with roentgenograms and photographs of a pathologic specimen. All the children showed symptoms developing immediately after birth. First noted were tenseness and protuberance of the abdomen; usually there were fever, cyanosis, and difficult respiration, and occasionally there was vomiting. Bowel movements usually were normal. The confirmatory diagnosis can be made by roentgenograms showing seropneumoperitonitis. The course is rapidly fatal.

GERSTLEY, Chicago.

URIC ACID INFARCT OF THE NEW-BORN: MICROCHEMICAL STUDIES. S. EHRLICH, Virchows Arch. f. path. Anat. **283**:194 (Jan. 4) 1932.

Histologic examination of the kidney of the new-born shows the presence of crystals chiefly in the straight tubules of the medulla. In a few cases the crystals were found in the tubules of the cortex. Histochemical examination of the kidneys reveals the presence of sodium, calcium, phosphoric acid, oxalic acid and chiefly uric acid as constituents of the "infarct." The theories concerning the formation of the uric acid infarct are discussed extensively, and the interrelation between infarct and secreting kidney-epithelium is stressed.

SHOENTHAL, New York.

IRRITATIVE CATARRH AND DACRYOCYSTITIS IN THE NEW-BORN. FRITZ JAEGERS, Ztschr. f. Geburtsh. u. Gynäk. **100**:42, 1931.

The irritative catarrh of the eyes in the new-born after the instillation of a silver preparation is well known, since this prophylactic method was started by Credé in 1881. The author believes that there is another important and much more dangerous illness of the eye in the new-born to which insufficient interest has been paid up to the present—a condition often mistaken for simple, irritative catarrh. This disease is dacryocystitis neonatorum congenita, purulent inflammation of the lacrimal sac. It is also often confused with gonoblennorrhea. Every case of persistent "irritative catarrh" is suspicious. The lacrimal duct becomes impenetrable instead of penetrable, as it should normally be. The inflammation is secondary.

The author saw during the last three and one-half years, among 5,000 new-born babies, 50 cases of irritative catarrh and 15 cases of dacryocystoblennorrhea. The therapy consists in management of the lacrimal sac. Seldom is an operation necessary. Early and suitable treatment is essential, as a secondary phlegmon can be perilous to the eyes of the child.

ADAIR and SIEDENTOPF, Chicago.

THE GASEOUS CONTENT IN THE BLOOD OF THE UMBILICAL CORD BEFORE AND AFTER THE BIRTH OF THE CHILD AND THE EXCHANGE OF GAS IN THE PLACENTA. G. HASELHORST and K. STROMBERGER, Ztschr. f. Geburtsh. u. Gynäk. **100**:48, 1931.

It has not been determined as yet whether or not the exchange of gas from the mother to the child, and vice versa, is brought about by a special activity of the placenta tissue or by diffusion of the differences in the pressure of the oxygen and carbon dioxide in the blood of the mother and fetus. To settle this question, the authors investigated the result of oxygen and carbon dioxide in four patients who were delivered by cesarean section. The blood flowing into and away from the uterus and the blood in the umbilical cord were examined. It was found that the tension of the oxygen in the venous blood of the mother was always from 5 to 23 mm. higher than that in the arterial blood of the child. Conversely the tension of the carbon dioxide in the arterial blood of the child was found in all cases to be from 4 to 14 mm. higher than that of the venous

blood of the mother. From these observations, one must conclude that the exchange of gas between the mother and fetus in the placenta is brought about normally by diffusion.

ADAIR and SIEDENTOPF, Chicago.

THE PATHOGENESIS OF ICTERUS NEONATORUM: THE IRON CONTENT OF THE LIVER IN THE FETUS AND IN THE NEW-BORN. KARL ADLER and M. ADLER, Ztschr. f. Geburtsh. u. Gynäk. **101**:128, 1931.

Investigations made on the decrease in the content of hemoglobin and in the number of erythrocytes in the new-born are not adequate methods of explaining the destruction of blood after birth. The authors therefore undertook investigations concerning the iron content of the liver in fetuses and in new-born infants. They found that the iron content in the liver of fetuses that died before the onset of labor pains was about the same as that of normal adults. During labor the iron content rises, more in immature fetuses than in mature children and more in heavily damaged offspring than in those born of easy labor. During the first days after birth more iron is stored in the liver. Later, the content returns to normal. Similar observations were made in experiments on rabbits.

ADAIR and SIEDENTOPF, Chicago.

THE CHANGES IN THE FREQUENCY OF THE FETAL HEART TONES DURING LABOR; THEIR CAUSE AND EFFECT ON THE CHILD. W. WILLIBALD, Ztschr. f. Geburtsh. u. Gynäk. **101**:724, 1932.

The author first discusses the literature regarding the changes of the fetal heart tones and the different theories of the origin. He then reports his observations in one hundred and ninety-four head presentations and thirty-nine breech presentations, in which the fetal heart tones were slackened under 100 or hastened over 160, or where an irregularity or any abnormality of the heart action was heard. He found that an acceleration of the heart tones from 160 to 170 per minute can take place for hours without danger to the child. There is a sign of danger only when there is an acceleration of more than 170 per minute.

The retardation of the fetal heart tones is unfavorable. It is as dangerous a sign during the second stage as during the first. Irregularity of the fetal heart tones is a serious sign of danger to the child, especially if an acceleration takes place after retardation. The cause of hastening of the fetal heart tones was illness of the mother, cord around the fetal neck and pressure on the head when passing the inlet of the pelvis. Pressure was the cause in most cases of slackening (87.8 per cent), but a disturbance of circulation was the cause in 12.2 per cent. The pressure on the skull was also the main cause in the cases of irregularity.

The author saw three cases with extrasystoles; this observation was without significance.

In cases of breech presentation, the pressure on the skull is not a very important cause of the alterations in the fetal heart tones. An irritation of the visceral nerves by the pressure of the thigh against the abdomen is probably the reason for an acceleration in such cases, but it is not a sign of danger.

ADAIR and SIEDENTOPF, Chicago.

Acute Infections

MEASLES CONVALESCENT SERUM. W. W. BAUER, Am. J. Pub. Health **2**:285 (March) 1931.

The author feels that the value of measles convalescent serum is such that an arrangement for collection and distribution should be made. Since its potency lasts only about six months, and since measles occurs at fairly regular and predictable intervals of from twenty-four to thirty months, varying in each community, serum cannot be held over this period. The author suggests a central

pooling point for a group of cities with a plan for withdrawing as necessity arises, each community supplying or withdrawing according to its relation to the cycle.

PARKER, Rochester, N. Y.

TONSILLECTOMY VERSUS MEDICAL TREATMENT IN CASES OF RHEUMATIC FEVER. WILLIAM H. ROBEY, M. Clin. North America **15**:875 (Jan.) 1932.

Tonsillectomy is an efficient means of stopping an attack of acute rheumatism when the usual purely medical measures have failed. The operation, even in the presence of fever and inflamed joints, is not more dangerous than interval tonsillectomies. It should not be done while active acute tonsillitis is present, but this question should seldom arise since acute rheumatism is usually a sequel of acute tonsillitis. The operation should be performed only by those having received special training. It is important to remove thoroughly all tonsillar tissue.

SMITH, Ogden, Utah.

HUMAN RABIES (REPORT OF TWO CASES). GUY F. CLEGHORN, New York State J. Med. **31**:1509 (Dec. 15) 1931.

Nassau County, N. Y., has been under quarantine for three years because of rabies. Two adults and four children were bitten by a rabid dog in May, 1930. In two of the children, aged 7 and 4 years respectively, rabies developed and the patients died. All the patients received antirabic serum given by the Semple method within forty-eight hours after injury. In one child the treatment was given daily for thirteen days; he died on the sixteenth day. The other child received twenty inoculations and died twenty-two days after being bitten. The wounds in these two cases were cauterized with phenol and mercurochrome-220 soluble. Fuming nitric acid is advised for the cauterization of all dog bites.

AIKMAN, Rochester, N. Y.

DIFFERENTIAL DIAGNOSIS OF MEASLES, SCARLET FEVER AND RUBELLA. SAMUEL S. WOODY, Pennsylvania M. J. **34**:307 (Feb.) 1931.

Because these three infectious exanthems exhibit certain symptoms in common, their differentiation may not easily be made in certain instances. With careful correlation of history and clinical manifestations, a correct evaluation of differences in incubation period, onset, course, distribution of the rash, infectivity, tendency to complication and sequelae and the employment of a differential blood count and of the Schultze-Charlton test, Woody believes that few errors in diagnosis should result. Scarlet fever is the most important of the three diseases, and when the patient is first examined very early or very late or when anginal symptoms are not marked or the eruption is faint its differentiation may be difficult. In no suspected case should a differential blood count be omitted. A case of scarlet fever should show leukocytosis, and often eosinophilia. The presence of Streptococcus hemolyticus in throat cultures is presumptive evidence only. Woody states that the Schultze-Charlton test is positive in 90 per cent of cases of scarlet fever.

HALL, Uniontown, Pa.

DIPHTHERIA IMMUNIZATION. H. J. BENZ, Pennsylvania M. J. **34**:372 (March) 1931.

In a statistical study of the morbidity and mortality from diphtheria in Pennsylvania, from 1906 to 1929, Benz finds, in 1906, a morbidity of 152 per hundred thousand of population. This ratio rose to 210 per hundred thousand in the years 1912 and 1913; it then dropped, with one rise to 144 in 1918, and in the next three years rose to the highest peak, 234 per hundred thousand in 1921, since which time there has been a steady downward trend to the lowest ratio recorded in

Pennsylvania, 75 per hundred thousand. The mortality rate during the twenty-nine year period has shown a steady downward trend from 34 per hundred thousand in 1906 to 6.8 per hundred thousand in 1929. The marked and steady decrease of the morbidity rate during the past six years Benz ascribes to the institution of general immunization of the preschool child by the employment either of toxin-antitoxin mixture or of the newer toxoid preparation of Ramon.

HALL, Uniontown, Pa.

CURRENT PREVALENCE OF COMMUNICABLE DISEASES IN THE UNITED STATES. Pub. Health Rep. **47**:651 (March 18) 1932.

From Jan. 31 to Feb. 27, 1932, the incidence of influenza and measles showed an increase, while meningitis and diphtheria were decreased. The incidence of scarlet fever was the same, with 23,442 cases. The average mortality was 12.3 per thousand.

SANFORD, Chicago.

TUBERCULOSIS AS A FACTOR IN THE MALIGNANCY OF SCARLET FEVER. O. MILLIAN, Arch. de méd. d. enf. **35**:129 (March) 1932.

Writing from the hospital for contagious diseases of children at Bucharest, Millian opens his exhaustive treatise on this unusual subject with the assertion that neither the etiology, the epidemiology, the physiopathology, the prophylaxis nor the treatment has been greatly clarified since the masterly theses of Sydenham and Trousseau. One feature of perennial interest in scarlet fever is the variability of type. After a period of benign invasions there suddenly appears, without discernible cause, a series of grave infections, septic, renal or cardiac. This phenomenon was illustrated in the epidemic of scarlatina at Bucharest in the early months of 1930, after several years during which the attacks had been relatively mild. It was noted that at autopsy in these malignant cases, extensive lesions of tuberculosis were present, but this was considered merely a coincidence until a more exhaustive study and a larger series of subjects impressed the observers with the idea of a causal relationship. Millian advances the view that the normal evolution of a benign or moderately severe case of scarlet fever is so altered and aggravated by the superimposed tuberculosis that the picture of a malignant process promptly develops. As long ago as 1862 Baginsky remarked that the prognosis of scarlet fever is unfavorable in tuberculous patients, and Hutinel has more recently reported necropsies in five malignant cases in which he noted more or less widespread lesions of pulmonary tuberculosis. Simonin has likewise called attention to this little known antagonism. Nine cases are reported by the writer in support of the contention that the coexistence of these infections may readily prepare the stage for a somber setting.

AMESSE, Denver.

PARAPLEGIA FOLLOWING MEASLES. L. BABONNEIX and F. B. LEVY, Bull. Soc. de pédiat. de Paris **29**:371 (July 1) 1931.

In a boy, 5½ years old, a flaccid paralysis of the extremities and sensory and sphincteric disturbances developed about one week after the onset of a typical measles rash. The possibility of this being either diphtheritic or poliomyelitic paralysis is mentioned, but not considered probable, and the conclusion is reached that this is a case of acute diffuse encephalomyelitis following measles.

BENJAMIN, Montreal, Canada.

ANTIDIPHTHERITIC VACCINATION BY THE CUTANEOUS ROUTE. A. BESREDKA, Compt. rend. Soc. de biol. **107**:1487 (Sept. 18) 1931.

An ointment containing 1 cc. of horse serum to each 10 Gm. of hydrous wool fat and liquid petrolatum was rubbed into the flanks of rabbits. From three to four

days later, to each 10 Gm. of ointment was added from 10 to 25 cc. of diphtheria antitoxin, and this mixture was rubbed into the flanks of the rabbits. At this time, a small quantity of antidiphtheritic serum (from 0.5 to 0.2 cc.) injected under the skin produced slight, if any, reaction.

Increasing doses of diphtheria toxin were applied in this manner for from twelve to fifteen days (i. e. as much as from 100 to 250 units of toxin was given). A local active immunity of the skin is produced, which leads later to a general passive immunity in the animal's blood.

WAHL, Cleveland.

THE RELATIONS BETWEEN NORMAL SERUMS POSITIVE TO THE DICK TEST AND THE SCHULTZ-CHARLTON PHENOMENON IN SCARLET FEVER. T. DUMITRESCO, S. BALMEZ and GROSSU, Compt. rend. Soc. de biol. **108**:321 (Oct. 16) 1931.

The authors, using eleven serums obtained from adults with positive reactions to the Dick test (not having had scarlet fever), performed the extinction test in fifteen frank cases of scarlet fever. Twenty-four hours following the injection, the test was positive in eleven of the fifteen cases. Three of the serums did not provoke the phenomenon in some of the cases, while in others the reaction was definite. There appears to be a question as to the absence of antibodies for streptococci of scarlet fever in the specimens of blood that gave a positive reaction. The Dick test and the Schultz-Charlton reaction do not agree in all persons, and further studies will elucidate the mechanism of the reaction.

WAHL, Cleveland.

ANTIDIPHTHERITIC SERUM AND ITS THERAPEUTIC ACTION AGAINST EXPERIMENTAL DIPHTHERIA INTOXICATION. G. RAMON, Compt. rend. Soc. de biol. **108**:488 (Oct. 30) 1931.

Ramon reviewed the protective effect of antidiphtheritic serum, by first injecting diphtheria toxin into 100 guinea-pigs, and then, at intervals, injecting antidiphtheritic serum. The dose of the toxin was fatal to the 400 Gm. animals used, but Ramon found that it was necessary to give the antitoxin within six hours after the toxin to promote recovery.

WAHL, Cleveland.

ANTIDIPHTHERIA IMMUNIZATION OF CHILDREN BY A SINGLE INJECTION OF PURIFIED AND CONCENTRATED ANTITOXIN. CLAUSE JENSEN, Compt. rend. Soc. de biol. **108**:528 (Nov. 6) 1931.

Jensen injected a single dose of 1 cc., corresponding to 150 units, of concentrated and purified antitoxin into institutional children from 3 to 8 years of age. In some fever and local reactions developed, but without severity. Immunity was established quickly in practically all cases up to one month after the injection. It is suggested that this method of immunization could be used in epidemics.

WAHL, Cleveland.

DURATION OF IMMUNITY AGAINST DIPHTHERIA PRODUCED BY A SINGLE INJECTION OF PURIFIED AND CONCENTRATED ANTITOXIN. CLAUSE JENSEN, Compt. rend. Soc. de biol. **108**:532 (Nov. 6) 1931.

Mathematical curves are calculated to show the course of immunization by concentrated and purified antitoxin (1 cc. equals 150 units) given as a single dose to infants. The curve of immunity reaches its height (a titer of 60) on the ninth day, and gradually recedes to a titer of less than 15 on the forty-fifth day. There is marked variance in the quality of immunity produced, and its duration varies from a few days to possibly a few years.

WAHL, Cleveland.

THE RELATION BETWEEN THE SCHICK TEST AND THE ANTITOXIN TITER OF BLOOD. CLAUSE JENSEN, Compt. rend. Soc. de biol. **108**:539 (Nov. 6) 1931.

The relative variance of opinion as to the amount of antitoxin in the blood necessary to produce a negative reaction to the Schick test is discussed from the evidence of many experimental lists. However, the results referable to one-thirtieth unit of antitoxin in the blood for the production of a negative Schick reaction have been noted in subjects artificially immunized, and the variance may then be considerable.

Jensen studied the blood antigen in his patients immunized by the concentrated antitoxin. He found that of 107 children (from 7 to 14 years of age) so immunized, 8 per cent gave positive reactions to the Shick test after one month. These 90 subjects were divided into two groups: 47 with markedly positive reactions showed a titer of less than 0.0005 unit, and 5 of this group had a titer greater than 0.003 unit. The subjects with positive Schick tests showing a moderate or feeble reaction had less than 0.0005 unit. Of the children with negative reactions to the Schick test (17), 4 had less than 0.0005 unit and the remainder 0.044 to 0.009 unit.

WAHL, Cleveland.

THE SCHICK REACTION AND THE ANTITOXIN TITER IN INFANTS VACCINATED BY A SINGLE INJECTION OF CONCENTRATED ANTIDIPHTHERIA SERUM. CLAUSE JENSEN, Compt. rend. Soc. de biol. **108**:543 (Nov. 6) 1931.

One cubic centimeter (150 units) of concentrated antidiphtheria serum was injected into several children. Twenty of them, six months later, had a titer between 0.0001 and 0.0005 and gave negative reactions to the Schick test. One child who gave a negative reaction had a titer of 0.0007 and one in whom the test was positive, a titer of 0.0004. Three others had a titer of 0.01. Therefore the fixed titer for the Schick test is not clearly shown.

WAHL, Cleveland.

THE IMPORTANCE OF A POSITIVE SCHICK REACTION IN INFANTS NOT IMMUNIZED AND IN INFANTS IMMUNIZED WITH DIPHTHERIA ANTITOXIN. CLAUSE JENSEN, Compt. rend. Soc. de biol. **108**:552 (Nov. 6) 1931.

Schick test toxin was standardized and the test read at two, four and seven days in 293 children (aged from 2 to 14 years). Immediately following the test, the titer was determined for antitoxin in Ehrlich units, and these values served as controls. Of 135 children who gave positive reactions, 89.6 per cent showed a titer of 0.0005. Thirty-two of these infants were given 1 cc. of concentrated diphtheria antitoxin, and showed a titer of from 0.03 to 0.0005.

WAHL, Cleveland.

A CASE OF TETANUS OF AURICULAR ORIGIN. R. C. AGUIRRE and J. A. GOMIS, Arch. argent. de pediat. **2**:440 (Aug.) 1931.

The authors report a case of a 2 year old child who introduced a grain of corn into the left external auditory canal. When the corn was removed several days later it was noted that the external auditory canal was somewhat eroded and that there was a slight perforation in the antero-inferior quadrant from which, however, no pus exuded. Several days after the removal of the foreign body there developed fever, rigidity of the neck, a left facial palsy and a marked trismus to which there were shortly added all other symptoms characteristic of tetanus, namely, risus sardonicus, dysphagia, opisthotonos, etc. The child died a few days later in spite of the use of Dufour's method of treatment, i. e., intrathecal administration of antitetanic serum under chloroform anesthesia.

The authors point out the difficulty of a differential diagnosis between tetanus of auricular origin and meningitis secondary to otitis media. They believe that trismus is more frequently a characteristic symptom of tetanus and is helpful in

the differential diagnosis. They recommend prophylactic antitetanic treatment in similar cases. They also point out that there are reports of only thirteen similar cases in the literature.

SCHLUTZ, Chicago.

A STUDY OF THE SCHICK TEST IN CHILDREN IMMUNIZED AGAINST DIPHTHERIA FROM FIVE TO SEVEN YEARS PREVIOUSLY. F. BAZAN, Arch. argent. de pediat. **2**:490 (Sept.) 1931.

The author repeated the Schick test in 131 children who were immunized to diphtheria between 1925 and 1928. Only children with previously positive Schick tests were immunized. This study showed that the immunity in the majority of these children persisted after several years. The results were, as follows: total number examined, 131; negative Schick tests, 124 (96 per cent); doubtful, 7, and positive, 0.

SCHLUTZ, Chicago.

A CASE OF FATAL ANAPHYLACTIC SHOCK FOLLOWING THE ADMINISTRATION OF ANTIDIPHTHERIC SERUM. M. T. VALLINO and F. DE FILIPPI, Arch. argent. de pediat. **2**:508 (Sept.) 1931.

The authors report the case of a 3 year old boy with diphtheria who died with the typical symptoms of anaphylactic shock almost immediately after the administration of 20,000 units of antidiphtheric serum.

There was a history of eczema in infancy and of scarlet fever a year previously for which the corresponding serum was administered without any ill effects.

SCHLUTZ, Chicago.

PYEMIA PARATYPHOSUS B CURED BY BLOOD TRANSFUSION. E. JACOBSON, Deutsches Arch. f. klin. Med. **172**:317 (Dec. 21) 1931.

The author reports the case of a patient with paratyphoid B infection who had a septic temperature and in whom numerous metastases developed in the form of subcutaneous abscesses and pyarthroses during the six months following the onset of the disease. The organism was recovered from abscesses. The infection cleared rapidly following two transfusions of blood.

DOOLEY, Kent, Conn.

TITER OF ANTITOXIN IN BLOOD OF PATIENTS WITH DIPHTHERIA AFTER ADMINISTRATION OF ANTITOXIN. M. WEICHSEL, Jahrb. f. Kinderh. **134**:129 (Jan.) 1932.

Diphtheria antitoxin, 500 units per kilogram, was injected into the muscle in a series of patients; the antitoxin titer of their serum was determined at twelve, twenty-four and forty-eight hours or thereafter. Less than one two-hundredth unit per cubic centimeter was present before the injection in cases of diphtheria, but in all cases from 2 to 4 units was present at forty-eight hours, and the amount at seventy-two hours was about one-fifth unit. The curves are nearly identical in controls, and in mild, severe, and toxic diphtheria. Antitoxin does not seem to be used up in diphtheria.

CLAUSEN, Rochester, N. Y.

IMMUNOLOGIC RELATIONSHIPS BETWEEN HERPES AND VACCINIA. HELMUTH FREUND, Zentralbl. f. Bakt. (Abt. 1) **11**:25, 1930.

Freund treated guinea-pigs intraperitoneally on five or six successive days with about 1 cc. of herpes antiserum obtained from rabbits infected intracorneally on several occasions with the virus. The guinea-pigs were then given intracutaneously, together with controls, vaccine virus, all injections being made into the plantar skin. The vesicles that developed were smaller and less well filled, and showed

a sharper line of demarcation in the serum-treated animals than in the controls. They also dried up more quickly in the former animals. These experiments confirm those of Gildemeister and his collaborators.

CANNON, Chicago. [ARCH. PATH.]

THE PURIFICATION OF DIPHTHERIA TOXIN AND ANATOXIN. I. A. TASMAN and A. B. F. A. PONDMAN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **72**:245, 1931.

The author gives a comparative review of the methods used for purification and concentration of diphtheria toxin and anatoxin, with selection of the "Alum-method," for which a detailed procedure is outlined. The end-product, which is a toxin and not a toxoid, is not as durable as the original solution.

DAVIDSOHN, Chicago. [ARCH. PATH.]

EVALUATION OF SCARLET FEVER ANTISERUMS BY BLANCHING. F. V. BORMANN and A. WOLFF-EISNER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **72**:411, 1931.

By comparative tests with various dilutions of different serums on the same patients the conclusion is arrived at that there is a direct relation between the ability of the serum to produce blanching of the cutaneous eruption and its therapeutic efficiency. Besides the dilution of the serum, the intensity and duration of the local effect must also be considered. The blanching phenomenon is due to a local antitoxic effect. (See articles by the same authors on the blanching phenomenon in *Ztschr. f. Kinderh.* **51**:550 and 560, 1931.)

DAVIDSOHN, Chicago. [ARCH. PATH.]

THE RELATIONSHIP OF THE VACCINE VIRUS TO THE MUCOUS MEMBRANES OF THE UPPER AIR PASSAGES. N. M. GOSCHANSKAJA, E. W. SKROTZKY and E. J. MUCHINA, Ztschr. f. Hyg. u. Infektionskr. **113**:358, 1932.

In sixty-three of sixty-five infants from 3 to 11 months of age, who were vaccinated, strong "takes" developed with accompanying angina which appeared on the third day and disappeared about the eighth day. On the fifth or sixth day after vaccination, throat swabs were made, and the material was rubbed on the corneas of guinea-pigs. In seventy-two hours, which the authors consider the optimum time for reading, ten of fifty-eight inoculated guinea-pigs showed a specific corneal reaction or keratitis, which indicates that the virus is present in the throat during active vaccinia.

WOLMAN, Chicago.

THE RETICULOCYTES IN DISEASES OF CHILDHOOD: I. MEASLES. M. KASAHARA and K. MAEDA, Ztschr. f. Kinderh. **52**:338 (Feb. 9) 1932.

The erythrocyte count is normal during the prodromal stages of measles, but increases during the exanthematous stage.

SHELLING, Baltimore.

PRESENT PROBLEMS IN SCARLET FEVER. A. LICHTENSTEIN, Finska läk.-sällsk. handl. **73**:89 (Aug.) 1931.

After a short review of the subject, the author describes the character of the late epidemics of scarlet fever in Sweden. He stresses the benign character of the disease during the last decennium, which he thinks may be the cause of the increase in frequency of the relapses observed during the last few years. He found that the frequency curve of positive Dick reactions coincided with the age curve of scarlet fever morbidity. Convalescent serum and scarlet streptococcic serum seemed to give equally good results, although neither influenced the occur-

rence of complications. Passive immunization with convalescent serum and antitoxin give only short immunity. Active immunization with scarlet streptococcic toxin caused many unpleasant reactions, and immunity developed slowly and uncertainly.

ELGHAMMER, Chicago.

Chronic Infections

TUBERCULOSIS AS IT AFFECTS CHILDBIRTH. JAMES ALEXANDER MILLER, Bull. Lying-In Hosp. **13**:297 (Feb.) 1932.

The author takes a definite stand against childbirth in cases of advanced pulmonary tuberculosis, as it carries with it a definite risk of the life of the mother and great danger of infection of the child. In such cases contraception, interruption of pregnancy and sterilization are proper professional procedures to be adopted according to the indications in each case.

In less advanced cases and in those in which the disease has become quiescent or arrested, the problem is less simple. Whether pregnancy can safely be tolerated depends on four factors: 1. The original extent of the lesion. The more advanced it is, the greater is the risk of relapse even if symptoms have disappeared. 2. The time that the patient has been without symptoms. The longer this is, the more favorable the prognosis, and after two years the risk becomes comparatively slight. 3. The manner of life of the patient. The more active the patient has been, without a relapse, the more likely it is that the strain of pregnancy will be similarly well borne. 4. The social and economic status. The patient who can be surrounded with every care is safer than a hard working housewife.

When pregnancy is not interrupted in patients with tuberculosis, especial management must be given in three periods: 1. The early months. If early toxemia of pregnancy, manifested for example by excessive vomiting, acidosis, etc., occurs, it may be necessary to revise a previous decision and to intervene on account of the possible untoward effect on the tuberculosis. 2. Delivery. This should be made as easy as possible. Cesarean section is preferable to a prolonged difficult labor. 3. The postpartum period. Nursing of the child should never be allowed, and lactation should be suppressed as soon as possible. A prolonged lying-in period of rest should be given, similar to that in a tuberculosis sanatorium.

KAISER, Rochester, N. Y.

LEPROSY IN CHILDREN. C. J. AUSTIN, J. Trop. Med. **35**:113 (April 15) 1932.

Of a total of 1,450 patients admitted to the leprosarium in nineteen years, 105 were under 15 years of age. Since 1918, 14 have been paroled as clinically and bacteriologically free for a period of two years. Two of them later had a relapse.

R. C. JAMIESON, Detroit. [ARCH. DERMAT. & SYPH.].

A CLINICAL AND ANATOMIC STUDY OF SOME OF THE EARLY FORMS OF PULMONARY TUBERCULOSIS IN INFANCY. P. F. ARMAND-DELILLE and C. LESTOCQUOY, Rev. franç. de pédiat. **7**:683 (Dec.) 1931.

By illustrative diagrams and thirty-one plates showing roentgenograms and pathologic specimens the authors present their conclusions that, besides the ordinary pulmonary tuberculosis of infancy, including the usual forms of small caseous areas and diffuse lesions as miliary tuberculosis, there exists a new clinical type which they designate as the "lobite." This consists in a tuberculous infiltration in only part of a lobe. This lesion exists with great frequency and must be considered as the commonest tuberculous lesion of infancy. It may progress in three ways: first, as a regression followed by a restitution; second, as an organization with sclerosis, and, third, by necrosis. Tuberculous pneumonia in young infants differs from that in adults in that often in the infant a greater part of the

lobe may be involved and there is less tendency to organization and sclerosis. In the past pulmonary tuberculosis in the infant was always considered fatal; now it may be considered as almost always curable.

SANFORD, Chicago.

THE EFFECT OF SOME CONTAGIOUS DISEASES ON TUBERCULOSIS IN INFANCY. G. COSTANTINO, Rev. franç. de pédiat. **8**:1 (Jan.) 1932.

The author has made an excellent review of the literature on the possible effects of malaria, syphilis, chickenpox, smallpox, scarlet fever, diphtheria, influenza, typhoid fever, pertussis and measles on tuberculosis. On the basis of this and of his own observations he concludes that it is practically impossible to evaluate these effects. On the whole, the influence of these conditions has probably been exaggerated, but in early infancy, when a massive infection may predominate, they would no doubt influence its virulence. Measles is the worst offender from this standpoint. From the existing evidence, measures should be taken to protect the child not only from a tuberculosis infection but from contagious diseases at an early age.

SANFORD, Chicago.

ROENTGENOGRAMS OF THE BONES OF SYPHILITIC PATIENTS IN EARLY INFANCY. M. PÉHU and A. POLICARD, Rev. franç. de pédiat. **8**:78 (Jan.) 1932.

The author presents twenty-four excellent roentgenograms illustrating osteochondritis, periostitis and epiphysitis.

SANFORD, Chicago.

THE RELATIONS OF HYDROCELE IN INFANTS WITH HEREDITARY SYPHILIS. M. POPOVICI-LUPA and FLORICA POENAREE, Spitalul **52**:211 (May) 1932.

According to the conception of Marfan, the form of hydrocele in the infant that is persistent, unilateral and irreducible should always make one suspicious of congenital syphilis. Other authors are more or less convinced of this fact. The writers have undertaken a serologic investigation from the point of view of the Wassermann and the Meinicke reaction in the blood and hydrocele fluid in eight infants. The same tests were given the mothers at the same time. The reactions, except one that was feebly positive, were all negative.

AUTHORS' ABSTRACT.

PERIFOCAL INFLAMMATION IN TUBERCULOUS CHILDREN. REINHOLD SELL, Arch. f. Kinderh. **94**:266 (Oct. 23) 1931.

The author discusses the different types of nonspecific infiltration of tissue that may occur about pulmonary tuberculous foci. He has observed and presents twelve cases of perifocal infiltration in which the focus is out in the lung field, nineteen cases of perihilar infiltration, ten cases of epituberculosis, four cases of peritracheal infiltration and eleven cases of infiltration with cavernous degeneration, the so-called *"Frühinfiltrat,"* which signifies the infiltration about a new tuberculous focus occurring in a previously infected person. The reactivity of the tissues is different in this case from that about a primary focus. The *"Frühinfiltrat"* has been considered the "ignition point" for pulmonary phthisis, in that the decay of the lung tissue makes the probability of a generalized reinfection from this point.

One regrets that this article is not accompanied by roentgen plates illustrative of the points discussed.

LESLIE, Evanston, Ill.

HIGH FEVER IN MILIARY AND PULMONARY TUBERCULOSIS IN CHILDHOOD WITH RECOVERY. GUNTHER PASCHLAU, Arch. f. Kinderh. **96**:94 (April) 1932.

The author reports the progress and cure of three cases of hematogenous miliary tuberculosis in small children. The therapy consisted in what was not done rather than in what was done.

Any form of stimulating treatment is to be avoided, particularly irradiation with sunlight or artificial lights, injections of tuberculin, or any foreign protein injection.

The fourth case at the time of the acute symptoms showed an infiltration about a tuberculous focus. As this cleared up rapidly, it was probably an allergic type of tuberculous pneumonia without a dissemination of tubercle bacilli into this area.

LESLIE, Evanston, Ill.

PROTECTIVE VACCINATION AGAINST TUBERCULOSIS. HERBERT BUSHMAN, Arch. f. Kinderh. **96**:147 (May 6) 1932.

The B C G strain of tubercle bacilli recovered from rachitic guinea-pigs, artificially infected, showed no increase in virulence, nor was any variation in virulence obtained from growth on various culture mediums. No harmful results were observed from injection of the B C G strain in 203 infants and children. The morbidity and mortality were below the figures for the nonvaccinated group. The subcutaneous route proved superior to the oral. Eighty-six per cent of those given subcutaneous injections showed positive reactions to B C G tuberculin, as against 76 per cent of those to whom B C G was administered orally. The percentage of those reacting to old tuberculin was considerably less.

Similar studies were made with the A. O. strain, and similar results were obtained. No increase in virulence was observed from the passing of the strain through rachitic guinea-pigs. No harmful results from injection were seen in 112 children. There were lowered mortality and morbidity in comparison with the nonvaccinated group, and 71.6 per cent of the subjects reacted positively to old tuberculin.

LESLIE, Evanston, Ill.

SYPHILIS AND PREGNANCY. RUDOLPH SPIEGLER, München. med. Wchnschr. **79**:95 (Jan. 15) 1932.

The Meinicke tests are helpful as controls for positive Wassermann reactions during pregnancy. Nonspecific serologic reactions occur during pregnancy and in other conditions in which there are increased intermediary metabolism and destruction of protein. The error from nonsyphilitic reactions can be reduced to a minimum (0.45 per cent) by using both the Wassermann and the Meinicke tests. On the other hand, pregnancy may cause a provocation of supposedly cured syphilis. This may become serologically evident late in pregnancy or only during the puerperium. For this reason Spiegler advises that all women who have had syphilis should receive antisyphilitic treatment while pregnant. The results in the prevention of congenital syphilis by proper treatment of the pregnant mother are excellent. A more difficult problem to decide is whether a new-born infant has syphilis. Negative serologic reactions in the blood of the umbilical cord do not exclude the possibility of congenital syphilis. Therefore, infants of syphilitic mothers who did not receive proper treatment during pregnancy should receive prophylactic treatment.

BRAHDY, Mount Vernon, N. Y.

EXPERIENCES WITH CHILDREN OF SYPHILITIC PARENTS. LUDWIG SPITZER, München. med. Wchnschr. **79**:97 (Jan. 15) 1932.

Spitzer reports his observations on children of syphilitic parents for over thirty years. The original material consisted of 700 families, for 158 of which the records are complete enough to permit detailed study. Thirty-two parents received mercurial inunctions and 46 both arsenic and mercury treatments (no details given). The youngest living patient is 10 years of age and the oldest is 24. Seventy-eight of the 158 couples remained sterile. A total of 117 children were born to the remaining 80 couples. Sixteen new-born infants had signs of syphilis at birth or within the first few weeks of life. The remaining 101 infants were apparently healthy at birth, but only 14 remained normal. Some of the abnormalities observed

are as follows: poor progress in school and poor physical development in 61 cases; mentally deficient or abnormal behavior in 9; epilepsy in 4; clubfoot in 3; stuttering in 2 and criminal tendencies in 4. In view of these unfavorable late results, Spitzer states that syphilitic persons should not have children. His conclusions in further detail are as follows: 1. The marriage of a syphilitic person to a healthy person is not advisable, but if it should occur, there should be no children. 2. If both persons are syphilitic, the marriage should be encouraged, because both might marry healthy persons, which would result in two unhealthy marriages. 3. If a man, who, according to the present knowledge, is considered cured marries a healthy woman, there is a possibility of healthy children. 4. If a mother is infected (even without evidence of the disease) and has given birth to a syphilitic infant, she will never have a healthy child. On the basis of these conclusions, and because with the present financial difficulties it becomes doubly difficult to support a useless person, sterilization of syphilitic parents is advocated.

BRAHDY, Mount Vernon, N. Y.

DIFFICULTIES IN THE EVALUATION OF B C G VACCINATION OF THE NEW-BORN. V. KRÁL, Časop. lék. česk. **69**:832 (May 30) 1930.

Except for possibly the United States and England, statistics on the death rate of tuberculosis among children and adults are lacking. Clinical diagnoses of death are not verified by autopsy in many cases. It is difficult to control the hygiene, environment and clinical survey of the immunized children. The author cites the rules of the Geneva conference on B C G: (1) There must be immunization of infants born of tuberculous mothers and living in a tuberculosis positive environment; (2) immunized children and their environment must be controlled and definitely reexamined; (3) statements of tuberculosis in the children and the environment must be accurately verified by known clinical methods, and (4) for accurate control it is best to have both a vaccinated and a nonvaccinated group under a similar environment, with frequent check-ups of both children and environment for a period of at least two years, but preferably of five years. All deaths should be verified by autopsy.

STULIK, Chicago.

A CASE OF PULMONARY TUBERCULOSIS IN A BABY. E. GORTER, Maandschr. v. kindergeneesk. **1**:265 (Feb.) 1932.

A typical example of the cure of a primary tuberculous complex is given.

VAN CREVELD, Amsterdam, Holland.

OPEN PULMONARY TUBERCULOSIS IN CHILDREN. H. D. DE BOER, Maandschr. v. kindergeneesk. **1**:377 (May) 1932.

The author investigated whether tubercle bacilli were present in the stomach: (*a*) in cases of active pulmonary tuberculosis; (*b*) in case of inactive pulmonary tuberculosis, and (*c*) in cases of tuberculosis of other organs in which involvement of the lungs could not be demonstrated. The stomach was washed during a period of fasting with 100 cc. of sterile water. The sediment of the washing fluid was examined for tubercle bacilli by Ziehl-Neelsen's method, by cultivation (Löwenstein) and by inoculation of rabbits.

Among twenty-nine children with active pulmonary tuberculosis the microscopic preparation gave a positive result in nine cases, the cultivation method in fifteen cases, and the experiment with rabbits in twenty-three cases. In some of these cases the experiment with rabbits gave positive results whereas physical and roentgen examination demonstrated only slight changes. In forty-seven children with inactive processes in the lung, tubercle bacilli were found only three times. Of the five children with tuberculosis of other organs only one gave a positive result. The author discusses the importance of these results.

VAN CREVELD, Amsterdam, Holland.

Internal Diseases

KIDNEY FUNCTION TESTS. F. H. LASHMET, J. Michigan M. Soc. **30**:260 (April) 1931.

A criticism of ordinary and popular tests for the function of the kidneys is given by the author. He proposes a test devised by Newburgh and Lashmet that is not open to the objections made to the other tests. It consists of putting the patient to rest in bed for a three day fore-period, on a definite diet, with 1,500 cc. of fluids daily, and at 6 p. m. of the third day stopping all intake of food and fluid until the following noon. The urine specimen from 10 a. m. until noon is tested for specific gravity. Twenty-five patients with normal and ninety-five with damaged kidneys were studied; all of the first group showed a specific gravity of 1.026 or above, and all but four of the second group failed to do so. By clinical observation the test was comparatively 36 per cent more accurate than the test of phenolsulphonphthalein excretion and 73 per cent more accurate than the determination of nonprotein nitrogen.

SMITH, Ann Arbor, Mich.

CHRONIC NEPHRITIS IN CHILDREN. M. COOPERSTOCK, J. Michigan M. Soc. **30**:350 (May) 1931.

Cooperstock uses Christian's three types — chronic nephritis with edema, chronic nephritis without edema and vascular hypertension progressing into nephritis — as the basis for a classification of the condition in children. He mentions the last class only briefly because of its rarity in childhood. The condition called renal rickets is grouped with chronic nephritis without edema, and the low calcium in the condition is explained on the basis of an improper balance of phosphates. Under chronic nephritis with edema is listed "nephrosis," and separate considerations of edema, albuminuria, hypertension, hematuria, the chemistry of the blood and basal metabolism are given. The author feels that the lowered basal metabolic rate usually reported in nephrosis is probably due to errors in calculation based on the presence of large amounts of edema. Evidence is adduced that nephrosis is perhaps not a separate disease but a stage in the course of nephritis. Lastly, the protein requirement in nephritis is stressed. A safe allowance of 1 Gm. of protein per pound (0.5 Kg.) of body weight is suggested.

SMITH, Ann Arbor, Mich.

HEART DISEASE IN RHEUMATIC FEVER. W. J. WILSON, J. Michigan M. Soc. **30**:765 (Oct.) 1931.

Wilson followed one hundred cases of acute rheumatic fever. Of eighty patients with the first attack of rheumatic fever, twenty-four had heart disturbances following; of fourteen with the second attack, eleven had heart disturbances following; and of six with the third attack, four had heart disturbances following. The electrocardiogram, which was taken in twenty cases, showed no prolongation of the P-R interval.

SMITH, Ann Arbor, Mich.

REGIONAL VACCINATION AT THE PORTAL OF ENTRY; ITS USE AGAINST COLON BACILLUS INFECTION. R. POINCLOUX and H. ARLOING, Arch. d. mal. de l'app. digestif **21**:937 (Oct.) 1931.

Regional vaccination at the portal of entry consists in the use of a good vaccine, either autogenous or stock, containing the microbes of the infection to be combated and the injection of this vaccine into the sensitized tissues that have served as a portal of entry for the pathogenic organisms, even when this portal of entry is distant from the organs to be cured and when the invasion by the microbes

occurred a long time before. Such a definition distinguishes this method from subcutaneous vaccination and from the local vaccination of Besredka.

This method has been used in about 500 cases. Many of them were complicated by gonococcus infections, a few with staphylococcus infections and the rest (98) with Bacillus coli. At first, injections were made in the anorectal mucosa, without result. When the injections were made higher up, toward the colon, the treatment was successful. A special proctoscope and syringe were used. The injections were made about 12 cm. above the anus in and under the mucosa, but not into the underlying muscle of the rectum. Care must be taken to avoid perforation.

The initial dose of the vaccine to be used, either autogenous or stock, was 0.5 cc., the following doses being 1 cc., 1.5 cc., 2 cc. and 3 cc. Each injection was made from twenty-four to forty-eight hours after the reaction caused by the preceding injection had subsided. The signs of such a reaction are characteristic and are those of a true slight illness. The incubation period lasts for an average of from one and one-half to two hours. The invasion phase is marked by general malaise. The temperature rises to 39 or 39.5 C. (102.2 or 103.3 F.) in from seven to eight hours after the injection. The height of the reaction is characterized by colic, distention and diarrhea occasionally, and sometimes by nausea and vomiting. This period lasts from twelve to twenty-four hours. Defervescence takes place by lysis over a period of from thirty-six to forty-eight hours, but may last from three to six days. The typical normal reaction subsides in from two to three days. Some patients have marked subjective reactions (colicky pains) without much fever (from 37.8 to 38 C. [100 to 100.4 F.]); others have very few symptoms until after the third or fourth treatment, when a marked reaction may occur. Some patients are improved or even cured after slight or delayed reactions. The authors state that they never observed an alarming reaction following injections made by the method they described.

Women having colon bacillus infection of the genito-urinary tract often have intestinal symptoms as well, obstinate constipation for the most part. Some have diarrhea and others have alternating diarrhea and constipation. Colon bacillus antivaccination made by injection into the rectal mucosa often has a salutary effect on the B. coli infection in the uterus and its adnexa, but always acts favorably on the intestinal element of the syndrome, the obstinate constipation or diarrhea clearing up. This leads the authors to look on this common condition as an infectious malady amenable to treatment quite different in principle from that usually used.

Fifteen case reports are given, which illustrate the results obtained by this method of treatment.

The article is interesting and convincingly written. TURNER, Chicago.

THE ELECTROCARDIOGRAM IN CONGENITAL HEART DISEASE. M. STEJFA. Arch. d. mal. du coeur **24**:478 (Aug.) 1931.

The author gives a short review of the literature and records several case histories. His conclusions may be summarized as follows: In principle, electrocardiography is a functional method. But as the form of the electrocardiogram depends considerably on anatomic structure, one must depend, with certain reservations, on the electrocardiogram in the diagnosis of the congenital diseases. The electrocardiogram, together with other clinical methods of examination, will give the following information:

1. An intense systolic murmur with its maximum intensity in the second left intercostal space near the sternum, even when unaccompanied by a thrill, is evidence of a marked right preponderance, a preponderance that cannot clinically be explained otherwise (for example, by kyphoscoliosis, mitral disease, pulmonary sclerosis or thickening of the pleura, fibrous tuberculosis, etc.), and may be considered as a symptom of congenital heart disease, without having formal roentgenologic verification.

2. When clinical examination leads to the diagnosis of a congenital lesion of the heart (because of cyanosis and a precordial thrill) and when the electrocardiographic tracing is normal, pulmonary stenosis cannot be considered because in all cases in which the diagnosis was verified at autopsy there has been found a right-sided preponderance. In the author's first cases in which the electrocardiogram was normal one must consider rather a persistence of the ductus arteriosus or Roger's disease or even lesions associated with atrophy of the right ventricle.

3. When the electrocardiographic examination of congenital heart disease shows an organic lesion of the bundle of His, or of the branch of the Tawara node, one must suspect a lesion of the interventricular septum.

TURNER, Chicago.

THE VAGOGASTROCARDIAC REFLEX AND ITS CLINICAL APPLICATIONS. C. FARMAKIDIS, Arch. d. mal. du coeur **24**:529 (Sept.) 1931.

The vagogastrocardiac reflex is described as follows: The patient lies on his back and the area of absolute dulness of the heart is percussed. At the same time the exact position of the cardiac apex is determined. The patient is then asked to bend the knees and flex the thighs on the abdomen, and while he breathes through his mouth so that the abdominal muscles are relaxed a prolonged massage of the abdominal region over the anterior surface of the stomach is made. The area of cardiac dulness is again percussed and there is found, in a certain number of persons, only a dilatation of the left side of the heart. The cardiac apex is displaced downward and outward; in other words, there is an increase of the longitudinal diameter of the heart. The phenomenon is sometimes of short duration, scarcely as long as it takes to tell about it, and sometimes it is delayed, in which case it is necessary to make repeated percussions of the area of cardiac dulness in order to detect any change.

Persons in whom the vagogastrocardiac reflex is positive have, for the most part, hyperchlorhydria with signs of vagal hypertonicity (hot flashes, increased salivation, hyperhidrosis, scanty, dry feces, etc.).

A number of these patients show dyspnea after fatigue or walking; others, on the contrary, have simple general asthenia without any evident sign of cardiac disturbances. Certain of these same persons show, after elicitation of the reflex, a rapid fall of the maximal arterial pressure; others show disturbances of conductivity (dropped beats, irregularities) or sometimes an abrupt slowing of the pulse, and lastly, some show a respiratory arrhythmia.

Farmakidis states that this reflex will enable one to discover latent hypotonicity of the left cardiac musculature, caused by various pathologic conditions (hypertension, intoxication, physiologic causes, etc.) at a time when all objective signs detectable by ordinary methods of clinical examination are absent.

TURNER, Chicago.

THE ANEMIA OF BRIGHT'S DISEASE. EUGENE TAREJEW, Arch. d. mal. du coeur **24**:627 (Oct.) 1931.

The author states that it is to the French school, and particularly to the great clinicians such as Widal, Labbé and Aubertin, that credit should be given for having called attention to the frequency and diagnostic value of severe anemia in renal insufficiency.

He sought an answer to the question as to the cause of the anemia of Bright's disease, and concludes that no hemolytic factor is involved. Rather, he is of the opinion that there is a decreased capacity for regeneration of the blood in the bone marrow, owing to the action of the uremic poisons, and that this is the principal cause of the anemia.

TURNER, Chicago.

ESSENTIAL CARDIAC HYPERTROPHY IN NURSLINGS. R. DEBRÉ and A. BUSSON, Arch. de méd. d. enf. **35**:65 (Feb.) 1932.

It has been well established that there exists in earliest infancy a pure, primitive, idiopathic or essential cardiac hypertrophy. These terms are used to differentiate this condition from the type produced by the common congenital malformations. Thus far only fifty cases of the disease have been observed, six of them being reported in the French literature. While the etiology has usually been ascribed to some unrecognized organic lesion, no serious study of the pathogenesis has been undertaken. In a case reported by the authors, it was found that the father and a paternal uncle of the infant had been stricken with blindness through atrophy of the optic nerve of an undetermined origin; syphilis was excluded. Various writers, among them Sprague, Bland and White, have found familial cardiac malformations, but usually the infant exhibiting the disease has appeared normal at birth and has gone through a portion of the first year in excellent health. Exceptions to this have been noted by Scott, Savage and Burghi in whose cases symptoms seemed to develop immediately after birth. In some instances, autopsy alone revealed the hypertrophy. Dyspnea is the most common symptom, often accompanied by retraction substernally and suprasternally, frequently of a paroxysmal nature; cough is not a constant factor, but cyanosis is a characteristic sign in all cases. Pallor is found in many instances; digestive disturbances are frequently noted; tachycardia is present in the majority of cases. However, the diagnosis rests entirely on the roentgenograms. The prognosis is utterly dark, a fatal issue usually being recorded before the end of the first year.

AMESSE, Denver.

AN EPIDEMIC OF ACETONEMIA IN CHILDREN OF BUENOS AIRES. L. VELASCO BLANCO, Arch. am. de med. **8**:10 (Jan.) 1932.

The clinical picture presented resembles closely that of meningitis or of tuberculous meningitis. In all of them there may be marked acetonemia. Observations on the spinal fluid are the chief aid in the differential diagnosis. The cases in which there are marked cephalomeningeal symptoms may terminate fatally.

The author believes that diet, especially an error in fat metabolism, is more frequently a causative factor in the development of the disorder than infection.

In the treatment, the administration of carbohydrate, especially dextrose or levulose, is of prime importance. The author also advocates the administration of insulin subcutaneously in a dosage of from five to ten units. It must be buffered with adequate amounts of carbohydrate, as the patients show marked hypoglycemia. A solution of dextrose must be given by other than oral routes in grave cases. The author prefers the subcutaneous and intraperitoneal routes to the intravenous.

SCHLUTZ, Chicago.

REPORT OF A CASE OF SUBACUTE ALEUKEMIC LYMPHADENOSIS. L. V. BLANCO and A. PUGLISI, Arch. am. de med. **8**:26 (Jan.) 1932.

The case reported occurred in a boy 12 years of age; it began with massive glandular enlargement in the submaxillary regions of the neck with rapid extension to both axillae and involvement of the inguinal glands. The spleen was markedly enlarged and extended to the umbilicus. The Mantoux tuberculin reaction was positive. The case terminated fatally. The blood picture, biopsy, study of the bone-marrow and, finally, autopsy showed the presence of immature forms of white blood cells of the agranulocytic and lymphocytic types and the picture of an aleukemic lymphadenosis. General hyperplasia of the hematopoietic system was the outstanding feature of the case. A lymphatic diathesis existed long before the onset of the active manifestation of the condition.

SCHLUTZ, Chicago.

PATHOLOGY AND CLINICAL SYMPTOMATOLOGY OF A CYST IN THE LUNG OF A CHILD. J. BONABA, Arch. de pediat. d. Uruguay **2**:217 (May) 1931.

The author recommends the production of pneumothorax in this condition. It should always be carried out if the case shows delay in spontaneous cure with persistent purulent expectoration, with or without hemoptysis and with or without fever and alteration of the general well-being of the patient. Clinical and roentgenologic evidence of cavitation and the formation of a pyoneumocyst are indications for this operative procedure. It is practically the only measure that assures a cure.

SCHLUTZ, Chicago.

TREATMENT OF HYDATID CYST IN THE LUNG OF A CHILD. PRUDENCIO DE PENA, Arch. de pediat. d. Uruguay **2**:263 (June) 1931.

Treatment must vary according to the situation and the size of the cyst. It is more difficult if the cyst is central than if it is peripheral. The operative procedure is carried out under local anesthesia in two stages. The first stage consists in resection of a rib and exploration of the suspected region. An attempt is made to form adhesions between the parietal thoracic wall and the lung before proceeding to the second stage. The second stage of the operation is undertaken sometime between the third and twelfth days. After careful clinical and roentgen examination has shown that there is no pleural effusion or acute pulmonary infection, the cyst is evacuated with a trocar, with the patient in a sitting position. This is done as gently as possible in order not to produce hemoptysis or bleeding after the operation. After the fluid ceases to flow from the cyst, the lung is incised down to the cyst and this opened freely. It is then marsupialized. Drainage is effected through tubes, and the cavity is packed with iodoform gauze for from two to three days.

General hygienic treatment and careful guarding against acute infections of the respiratory tract is essential in the after treatment. The final results in the case are checked up by roentgenologic observation. The outcome has been favorable in most cases.

SCHLUTZ, Chicago.

THE TREATMENT OF CROUP. JUAN JOSÉ LEUNDA, Arch. de pediat. d. Uruguay **2**:283 (June) 1931.

It is very essential to establish the differential diagnosis between true croup and false croup. The one must be treated by the use of diphtheria serum, the other by the use of antiphlogistics during the period of dyspnea and by many antispastic remedies at a later period.

In the first, the author prefers intubation to tracheotomy. For threatened asphyxia the results are much more uncertain and unfavorable with tracheotomy. If there is a great deal of laryngeal infection and inflammatory edema, the authors prefer tracheotomy to intubation. Indirect laryngoscopy should be used for the laryngeal examination. In the hands of the unskilled, tracheotomy is to be preferred to intubation, as it is apt to produce less trauma.

SCHLUTZ, Chicago.

HYDATID CYST IN THE LUNG OF THE CHILD. VICTOR ESCARDO Y ANNAYA, Arch. de pediat. d. Uruguay **2**:519 (Nov.) 1931.

There are four types of cyst which occur in the lung of a child: round, oval, lemon-shaped and an irregular form. The first and second types are most frequent.

When the cyst is large, it may occupy all the pulmonary area. Those of smaller size are usually seen as a round or convex zone in the clear part of the lung. The superposition of the cystic and cardiac shadows sometimes produces shadows in the form of sandglass or a camel's hump. The small cyst is the size of a hen's egg; the medium-sized is as large as a medium-sized orange; the large ones may occupy half of the field of the lungs. Multiple cysts in one lung are sometimes found.

Small cysts of the left base may remain hidden by the heart. The differential diagnosis of pleural effusion, malignant tumors and pulmonary metastasis must be considered. The association of the cyst with pulmonary or pleural processes often renders the diagnosis difficult.

The roentgenologic picture also varies somewhat if the cyst is evacuated by vomiting, which alters its shape and size. Roentgenology is one of the most important aids to the surgeon in the location of the cyst. Pneumothorax is a rare complication.

SCHLUTZ, Chicago.

PROTOZOA PARASITES IN THE CHILDREN OF MONTEVIDEO. A. GAMINARA and R. V. TALICE, Arch. de pediat. d. Uruguay **2**:531 (Nov.) 1931.

This study includes one thousand pupils in the schools of Montevideo, all of whom were apparently healthy. Only fresh feces were examined. Infection was found in 43.6 per cent. In the interior of the country, the infection reached only 38.67 per cent. Giardia, the parasite most commonly found (in 21 per cent) frequently produced a chronic diarrheal condition. Each child was examined only once.

SCHLUTZ, Chicago.

A FORM OF UREMIA SIMULATING ACUTE MENINGITIS. LUIS MORQUIO, Arch. de pediat. d. Uruguay **2**:590 (Dec.) 1931.

This condition occurred in a boy 13 years old. All the symptoms of acute meningitis were present. No bacteria were found in the clear spinal fluid. The appearance of hematuria and the development of a uremic state revealed the true cause of the strange array of symptoms. Complete cure followed the usual treatment for uremia and the underlying glomerular nephritis.

SCHLUTZ, Chicago.

PYURIA IN THE YOUNG CHILD. WALTER HEYMANN, Ergebn. d. ges. Med. **15**:307, 1931.

The author adopts a classification of pyurias which is a modification of that of Aron. Acute pyurias are divided into (*a*) the septic forms, which may be primary or secondary, and (*b*) the forms which occur as acute or subacute complications or sequelae of the dystrophies, infections or disturbances in weight (dehydration pyuria). The chronic subfebrile or afebrile pyurias are subdivided into those which are residual from the acute forms and those which are the result of other localized diseases or anomalies of the genito-urinary tract. A primary form of the acute septic type is listed because of its characteristic clinical picture, but the author believes that etiologically these conditions are all secondary either to infectious or to nutritional disturbances.

A full description of the clinical and laboratory observations in each type of pyuria is given, and various forms of therapy are discussed. Alkali therapy is still the most dependable, but more important than the administration of drugs is the treatment of the underlying nutritional condition. Much is still to be learned regarding the prognosis for permanent cure in these cases.

CRANE, Chicago.

THE NONDIABETIC GLYCOSURIAS AND HYPERGLYCEMIAS OF THE OLDER CHILD. G. FANCONI, Jahrb. f. Kinderh. **133**:257 (Nov.) 1931.

The author gave from 20 to 30 Gm. of dextrose in a glass of water at 8, 9 and 10 a. m., and at 11 a. m., from 0.3 to 0.8 mg. of epinephrine. Blood sugar was given by the Bang method at 8, 8:20, 8:40, 9, 9:30, 10, 10:30 and 11 a. m. and then every half hour "into the afternoon." The "hyperglycemia mean value" was calculated from the first eight doses. The absence of a rise in the blood sugar after the second or third dose of dextrose is due to the increased secretion of insulin

and is termed the "Staub effect." A study of two families with "renal glycosuria" showed that the various forms distinguished by Salomon merge into one another. No case of true diabetes was found in these families. The rise of the curve for blood sugar was less than normal, the Staub effect was most pronounced, and the hyperglycemia mean value was low. A case of the nephrotic form of renal glycosuria was studied. Among the types of glycosuria and hyperglycemia due to nervous disorders, the author describes several cases of hyperglycemia in Feer's (Swift's) disease and in infants with "intoxication." Among those due to a previous lack of carbohydrates, he discusses especially cyclic vomiting.

CLAUSEN, Rochester, N. Y.

EXPERIMENTS WITH B COLI ENDOTOXIN. ROSEL GOLDSCHMIDT, Jahrb. f. Kinderh. **133**:346 (Nov.) 1931.

An attempt to repeat the work of Plantenga revealed the fact that the filtrate from a culture of Bacillus coli is toxic and that the various toxic elements cannot be distinguished.

CLAUSEN, Rochester, N. Y.

SPRING CATARRH. K. STOLTE, Jahrb. f. Kinderh. **134**:6 (Dec.) 1931.

Stolte describes a few cases of infection of the upper respiratory tract that followed exposure to sun and quartz lamp. He thinks that the condition may be due to a sudden change in mineral metabolism, that is, to lowered calcium and increased potassium in plasma and tissues, which causes swelling of the tissues. A temporary "exudative diathesis" can thus be brought about.

CLAUSEN, Rochester, N. Y.

THE EFFECT OF INTRAMUSCULAR INJECTIONS OF BLOOD IN INTERLOBAR PLEURISY AND OTHER RESPIRATORY DISEASES. BERTA BALS, Jahrb. f. Kinderh. **134**:51 (Dec.) 1931.

This article is recommended because of the simplicity of the technic employed and because of the apparently excellent results in eleven cases. No comparison is made with cases in which other treatment was used.

CLAUSEN, Rochester, N. Y.

FIBROSIS OF THE ENDOCARDIUM IN EARLY INFANCY. KÄTHE BECKER, Jahrb. f. Kinderh. **134**:64 (Dec.) 1931.

The author reports a case with autopsy. The mother suffered from thrombophlebitis during the last month of pregnancy. The infant, at first apparently well, developed signs of circulatory failure at 1 month of age and died at 3 months. Extensive fibrosis of the endocardium, thrombotic in nature, was found.

CLAUSEN, Rochester, N. Y.

A DISEASE RESEMBLING SODOKU (RAT-BITE FEVER), CAUSED BY THE BITE OF A FIELD-MOUSE. ELISABETH JUNGBLUTH, Jahrb. f. Kinderh. **134**:85 (Dec.) 1931.

A boy of 9 years was bitten on the thumb by a field-mouse. Two weeks later the wound became inflamed; a temperature of 42 C. (107.6 F.), lymphangitis, lymphadenitis and thrombophlebitis developed. The course was marked by repeated attacks of high fever of one or two days' duration and morbilliform rash. No spirochetes were found. Intravenous injections of "Germanin" were ineffective. Ultimate recovery was effected in about three months.

CLAUSEN, Rochester, N. Y.

SEVERE LIPEMIA IN A DIABETIC CHILD. ELISABETH JUNGBLUTH, Jahrb. f. Kinderh. **134**:102 (Dec.) 1931.

The blood of a boy of 9 years in a diabetic coma looked like "chocolate" and contained 21.2 per cent fat. The fundi showed marked changes. The lipemia disappeared with the relief of the coma, and a fat meal caused only normal elevation in the fat of the blood.

CLAUSEN, Rochester, N. Y.

PRIMARY CHRONIC POLYARTHRITIS OR ARTHRITIS DEFORMANS. V. SLIFERAITE, Kinderärztl. Praxis **2**:292 (July) 1931.

This disease is rare and must be sharply differentiated from chronic secondary rheumatic arthritis. The latter shows an acquired heart lesion in from 60 to 90 per cent of the cases, while in the former heart lesions practically never occur. Ibrahim reported that 73 per cent of his fifty-seven patients with arthritis deformans were under 6 years of age, while 55 per cent were under 4 years. The roentgenogram shows progressive disappearance of the cartilage and atrophy of the bone. Secondary atrophy of the muscles may be exceedingly marked. There are three theories as to the etiology: the neurogenic theory (Charcot), the metabolic theory, that the condition is due to a metabolic disturbance (Johannessen), and the infectious theory, to which the author subscribes. The disease usually begins with a fever, which recurs at intervals and is accompanied by nasopharyngitis. The treatment consists of salicylates, warm salt baths, diathermy and injections of a proprietary protein preparation. The prognosis is good as to life but poor as to complete recovery. The author reports two cases, that of a boy of 12 years and that of a girl of 18 months.

HUENEKENS, Minneapolis.

ACUTE POLYARTHRITIS IN CHILDHOOD AND ITS TREATMENT. JOSEPH GEHRT, Kinderärztl. Praxis **2**:385 (Sept.) 1931.

The author recommends large doses of salicylates in the form of acetylsalicylic acid, from 4 to 6 Gm. a day. The dosage is gradually reduced to 1.5 Gm. per day and continued for from four to six weeks. No bad effects are noticed, except perhaps excessive sweating. The most effective remedy for the pain is intramuscular injections of a solution of atrophan, 0.5 Gm., and sodium salicylate, 0.5 Gm., plus a small amount of procaine hydrochloride. Two injections are given the first day, followed by a single daily injection for the next three or four days. If an idiosyncrasy against salicylates exists, amidopurine may be used in doses of 0.3 Gm. four times a day for the first day, three times a day for the second day and therafter twice a day for from two to three weeks. The joints are wrapped in cotton, with or without the addition of sulphonated bitumen N. F. or a petrolatum preparation. Tonsillectomy has not proved effective in preventing cardiac complications. Oral sepsis as a focus of infection has not been sufficiently explored.

HUENEKENS, Minneapolis.

OBSERVATIONS IN A CARDIAC CLINIC FOR SCHOOL CHILDREN. H. SACHS, Med. Klin. **27**:134 (Sept. 11) 1931.

This is a statistical and clinical report of the work in a Berlin school clinic for children with cardiac disease. It does not contain anything new but is an interesting presentation of the subject.

ZENTAY, St. Louis.

CLINICAL STUDIES OF THE ANTI-ALLERGIC TREATMENT OF ASTHMA, ECZEMA AND HAY FEVER. H. T. SCHREUS and E. WILMS, München. med. Wchnschr. **78**:831 (May 15) 1931.

The authors used small doses of roentgen rays for the treatment of asthma, eczema and hay fever. The majority of patients were entirely relieved of

symptoms or greatly improved. Skin tests with allergins were made before and after treatment in several cases. Most of the reactions were weaker after treatment.

BRAHDY, Mount Vernon, N. Y.

SYMPTOMLESS OCCURRENCE OF TUBERCLE BACILLI IN THE TONSILS IN RECURRENT RHEUMATIC POLYARTHRITIS AND RETROBULBAR NEURITIS. K. AMERSBACH, A. LÖWENSTEIN and E. LÖWENSTEIN, München. med. Wchnschr. **78**:1078 (June 26) 1931.

Tonsillectomy was performed on sixteen patients with recurrent rheumatic polyarthritis. All the patients were free from tuberculosis on physical examination. No tubercle bacilli were found in smears from the surface of the tonsils or in blood cultures. No tuberculous changes were found on histologic examination of the tonsils. However, in five of fourteen cases studied completely, tubercle bacilli were found on culture of the tonsillar tissue. This is additional evidence which Löwenstein and his associates bring out to show the relation between the presence of tubercle bacilli and certain cases of recurrent polyarthritis.

BRAHDY, Mount Vernon, N. Y.

PERITONITIS DUE TO ASCARIS LUMBRICOIDES. G. B. GRUBER, München. med. Wchnschr. **78**:1129 (July 3) 1931.

A boy, aged 3 years, after the administration of santonin for intestinal parasites, passed sixty worms. A month later he made an uneventful recovery from measles and pneumonia. Some time later his abdomen became enlarged, and there were recurrent colic and fecal vomiting. Laparotomy was performed, and the child died an hour later. There was purulent peritonitis with many parasites free in the abdominal cavity and some enmeshed in the mesentery. Careful postmortem examination of the intestines failed to reveal any perforation or inflammatory areas. This case illustrates the passages of Ascaris through the normal intestinal wall without leaving evidence of a perforation.

BRAHDY, Mount Vernon, N. Y.

THE ETIOLOGY OF PERICARDITIS. A. A. GERKE, Virchows Arch. f. path. Anat. **278**:1, 1930.

For his study Gerke used 75,856 clinical and 26,771 necropsy protocols of the past twenty years. These were taken from institutions in Moscow that had been under the direction of the same school of pathology. The material included 4,442 records from a hospital that received chiefly cases of sepsis. In this large material there were 1,756 cases in which pericarditis was found. The author summarizes these cases as follows: rheumatic infection (including valvular and myocardial lesions presumably due to rheumatic infection), 336 cases, or 19.1 per cent; tuberculosis, 275 cases, or 15.6 per cent; pneumonia and pneumococcal pleuritis, 251 cases, or 14.2 per cent; nephritis, 151 cases, or 8.6 per cent; sepsis, 301 cases, or 11.4 per cent; miscellaneous conditions, 411 cases, or 23.1 per cent; conditions the etiology of which was unknown, 43 cases, or 2.4 per cent. Cases of simple hydropericardium are not included. The interesting data relating to the incidence of pericarditis in various disease groups can be only briefly indicated. In 1,634 cases of pneumococcal infection in which necropsy was performed, there were 334 examples of pericarditis. The latter condition was associated more often with pneumonia of the lower lobes than with that of the rest of the lungs, and most frequently with consolidation of the anterior part of the left lower lobe. In 128 cases of influenza in which necropsy was performed, pericarditis was detected 23 times. The influenza bacillus was not isolated in any case, a fact that the author thinks may be due to the hurried technic of the war years, during which period most of the necropsies were done. The relative infrequency of pericarditis in sepsis is indicated by the occurrence of 149 pericardial involvements in a total of 5,359 cases of erysipelas, scarlet fever and septicemia, the latter chiefly of genital origin in women. In contrast to this is the high incidence of pericarditis in purulent tonsillitis; of 10

fatal cases coming to necropsy, all showed pericarditis; in addition, pericarditis was detected clinically 36 times in cases of tonsillitis that did not come to necropsy. Pericarditis was seen 81 times at necropsy in association with cancer, but was detected clinically in only 7 of 2,214 cases of tumor. Gummatous pericarditis was found in 12 of 28 cases in which death was ascribed to syphilis. The rarity of pericarditis as a complication of certain diseases is shown by its occurrence only once in 26,771 cases of gonorrheal infection and not once in 4,010 clinical and 639 cases of typhoid that came to necropsy. SCHULTZ, Chicago. [ARCH. PATH.]

THE PROBLEM OF INFECTIOUS SYSTEMIC DISEASES OF THE RETICULO-ENDOTHELIAL APPARATUS IN CHILDHOOD. H. U. GUIZETTI, Virchows Arch. f. path. Anat. **282**:194, 1931.

A 3 month old infant, weighing 5.8 Kg., was admitted to the hospital with the signs of a severe infection of the upper respiratory tract and otitis. The child had nosebleeds twice and showed a few petechiae on the tongue and cheeks. The spleen was felt as a hard tumor several fingerbreadths below the margin of the ribs. The blood showed a diminution of the red cells and hemoglobin, poikilocytosis, microcytes and macrocytes, 15,000 leukocytes and no immature white cells. The urine showed a trace of albumin, leukocytes and erythrocytes. The child was dyspneic; hemorrhages developed on the hands and feet, the dyspnea increased, and physical signs in the lungs were present the day before death. The child died suddenly with signs of bilateral emphysema of the neck. A roentgenogram of the right humerus showed a cystlike formation at the end of the diaphysis. At necropsy, nonhemolytic streptococci were obtained from the spleen. A very marked granulation of large cells in the spleen, liver, thymus, lungs, bone marrow and bones was found. These cells were considered (depending on the organ in which they were found) either as descendants of reticulum or endothelium cells, or as derived from histiocytes or fibrocytes, respectively. A few similar cases in the literature were discussed, and the disease was considered as an "infectious reactive hyperplasia of the reticulo-endothelial system."

SCHOENTHAL, New York.

ROENTGENOLOGIC DIAGNOSIS OF CHRONIC LEAD POISONING IN INFANTS AND SO-CALLED MENINGITIS. M. KASAHARA, Jikken Iho J. Exper. Med. **18**:146, 1931.

In about fifty cases of chronic lead poisoning in infants and of so-called meningitis due to lead, the author found peculiar shadows at the ends of long bones (humerus, radius, ulna, femur, tibia, fibula and anterior ends of the ribs). These shadows have sharp borders, and measurable width; they are of uniform density and transverse in position. They do not seem to appear in cases of lead poisoning in adults. The majority of the fifty patients in whom these shadows were found were young infants, the oldest with positive findings being 2 years and 8 months of age. Later studies may explain why the shadows are not seen in children over 3 years of age. These shadows are also found in short bones of the hand and foot. All these evidences point to the fact that the dense shadows are produced at the rapidly growing portions of the bones. From these observations, it is possible to regard roentgen examination of the bones as an important means of diagnosis in chronic lead poisoning.

KATO, Chicago.

Nervous Diseases

MENINGITIS MASKED BY ENCEPHALITIC SYMPTOMS. A. LEVINSON, Arch. Pediat. **49**:6 (Jan.) 1932.

The writer calls attention to the unilateral symptoms of encephalitic nature occurring in the course of meningitis. Five cases of meningitis (one of tuber-

culous, two of meningococcic and two of streptococcic meningitis) are reported in which the meningitis was masked by encephalitic symptoms. Coexisting encephalitis, which was demonstrated microscopically, is offered as an explanation for the encephalitic symptoms in these cases. At autopsy changes characteristic of encephalitis, as evidenced by the perivascular infiltration of the brain, were found.

It is further pointed out that not all unilateral symptoms in meningitis are necessarily due to encephalitis. It seems likely that recognition of the meningeal exudate in some cases may be responsible for unilateral symptoms. This is especially so when unilateral Brudzinski, Babinski and Kernig signs are present.

WADDELL, University, Va.

TWO CASES OF ATYPICAL FAMILIAL DYSTROPHY. GARRY DE N. HOUGH, New England J. Med. **206**:396 (Feb. 25) 1932.

Two cases in one family are reported from the Shriners' Hospital for Crippled Children in Springfield, Mass., with a detailed account of the progress of the disease in each case.

One was in a girl of 12 years, the only female in a series of 42 patients treated at the hospital; the other in her brother, two years her junior, who was admitted when 14 years of age. Both parents and three younger children were normal.

Both patients showed rather marked equinus deformity, which necessitated surgical correction. The girl's symptoms began at 7 years, with difficulty in running. The boy had experienced difficulty in going up stairs for three years, but had been unable to stand on his heels for some time before that.

The author describes the cases as clinically representing "a transitional form between the Duchene and the Leyden-Moebius types, pseudohypertrophic masses being present in one case and absent in the other."

Both children were given the pilocarpine and epinephrine hydrochloride treatment after operation, with apparently good results, especially in the case of the boy which was of shorter duration. This is in accord with previous results at the hospital, where about 50 per cent of the cases, particularly those seen early, have shown some definite benefit.

GENGENBACH, Denver.

TREATMENT OF INFECTIONS OF THE CENTRAL NERVOUS SYSTEM BY FORCED SPINAL DRAINAGE. GEORGE M. RETAN, New York State J. Med. **31**:1378 (Nov. 15) 1931.

Hypotonic sodium chloride solution is injected slowly into the blood stream, and at the same time the spinal fluid is drained continuously through a needle. The passage of fluid from the blood washes the perineural spaces. From 1,000 to 2,000 cc. of 0.45 per cent sodium chloride solution was given intravenously, and spinal drainage was continued for many hours. Plain water was also given freely by mouth and rectum.

The author reports the successful treatment of a patient with a severe case of poliomyelitis by this method. Good results were also obtained in a severe case of encephalitis and also in a case of syphilitic meningitis. Three patients with septic meningitis died. The author feels that this method of treatment is theoretically sound and that it is also safe

AIKMAN, Rochester, N. Y.

OBSERVATIONS ON THE TREATMENT OF MENINGITIS. GEORGE M. LYON, West Virginia M. J. **28**:193 (May) 1932.

Replacement of the cerebrospinal fluid by a potent antimeningococcic serum was practiced in the following manner: Lumbar puncture needles were introduced simultaneously into the spinal canal and into one or both cerebral ventricles. To the spinal needle was attached an empty 100 cc. Luer syringe by means of a flexible tube, and to the ventricular needle a similar syringe containing the serum.

By gravity plus, the fluid was withdrawn into the empty syringe as the serum was slowly injected into the cerebrospinal spaces, a bit less of the serum being injected than of the fluid withdrawn.

Normal intraspinal pressure was secured by slight drainage from the needles. The treatment was repeated in forty-eight hours. Between these treatments, and at less frequent intervals after the second treatment, spinal drainage was performed for relief of the patient and for study.

The cerebrospinal fluid was sterilized in from twenty-four to forty-eight hours after the first substitution treatment.

The method is admittedly radical, but justified by the high mortality in these cases following the usual methods of treatment.

SHAWKEY, Charleston, N. C

SOME THOUGHTS ON THE TERM ACUTE DISSEMINATED ENCEPHALOMYELITIS AND ITS AFFINITIES. OLIVER LOTHAM, M. J. Australia **2**:677 (Nov. 28) 1931.

The typical lesions of postvaccinal encephalomyelitis consist of: (1) congestion and hemorrhage; (2) perivascular mononuclear infiltrations, which may be remarkably slight, and (3) usually, but not necessarily, a more outlying perivascular demyelinization affecting both gray and white matter. Demyelinization in large areas is a striking but not essential accompaniment of the encephalitis or of the myelitis. As similar lesions occur in the course of measles, mumps, chickenpox, smallpox, influenza, antirabic treatment and other less defined diseases, and may even be reproduced by chemical means in the central nervous system of animals, it is quite likely that postvaccinal encephalomyelitis is not a disease of specific entity. The pathologic picture of acute disseminated encephalomyelitis (of vaccinal or other origin) as well as other forms of encephalitis with which it has affinities, such as acute multiple sclerosis, encephalitis lethargica and dementia paralytica, probably is an expression of similarity of brain reaction, no matter what the trauma.

Regardless of the causal agent, be it the germ of a particular exanthem or specific virus that creeps in, the lesions found in all these diseases with so much in common are evidently due in some instances to a neurotoxin, but the rôle of impaired vascular function, such as takes place in syphilis through narrowing by reason of the action of the spirochetes on the inner coats of the blood vessels, must not be overlooked.

GONCE, Madison, Wis.

A CASE OF TETANY WITH DISTURBED RELATION OF THE BLOOD CHLORIDES. RIBADEAU-DUMAS, R. MATHIEU, M. LEVY and GUIDI, Arch. de méd. d. enf. **35**:85 (Feb.) 1932.

These clinicians report a case of tetany in an infant of 9 months, with a history of repeated infections of the upper respiratory tract accompanied by parenteral diarrhea. Rickets in an aggravated form developed in spite of careful nursing and the use of cod liver oil; the tetanic manifestations were of the classic type, and hematologic examinations showed a gross departure in the relation between the globular and the plasmic chlorides. Treatment consisted of excessive doses of sodium bicarbonate.

AMESSE, Denver.

MENINGITIC FORM OF HEINE-MEDIN DISEASE. P. NOBÉCOURT, Progrès méd., Jan. 9, 1932, p. 54.

The author presents the case of a 9 year old boy who had typical symptoms of meningitis. The diagnosis was cleared by finding only 4 lymphocytes in the spinal fluid. Poliomyelitis is not confined in its pathologic processes to the anterior horn cells, but may affect the entire cerebrospinal system. Such cases resemble meningitis, and spinal puncture offers the diagnostic difference.

SANFORD, Chicago.

CONSIDERATIONS ON A CASE OF TUMOR OF THE ANTERIOR CRANIAL FOSSA IN A FEEBLEMINDED PATIENT WITH ENCEPHALOPATHY AND ACROMEGALY BUT WITH INTEGRITY OF THE HYPOPHYSIS. CARMELO VENTRA, Arch. gen. di neurol., psichiat. e psicoanal. **12**:72 (March 31) 1931.

The author describes the case of a feebleminded epileptic woman. In early infancy she had meningitis and became mentally defective; she learned to talk at 10 years, but always had a grave defect in speech. At the age of 15, on the background of mental deficiency, she began to show symptoms of mental disturbance. Menstruation began only at the age of 17, and the periods were irregular. She had a masculine aspect and presented symptoms of acromegaly. At the age of 30, she began to have severe generalized epileptic fits; later headache, vomiting, mental apathy and ophthalmoplegia developed. She died at the age of 45. At autopsy evidences of chronic leptopachymeningitis, especially at the base, with intense meningeal congestion were found. In the anterior cranial fossa, underneath the frontal lobes, there was a lobulated tumor weighing 125 Gm., the size of an orange. The hypophysis was normal. Histologic examination of the tumor revealed a glioma. Histologic examination of the hypophysis did not reveal an abnormality. After a detailed discussion of the case, the author states that the diagnosis of intracranial tumors, difficult in general, becomes even more problematic in patients with mental disturbances, because of the difficulty of discriminating between symptoms due to the tumor and those due to the associated mental disease. Among the general symptoms of cerebral tumor, epilepsy of the essential type may develop early and for years remain the only symptom of a tumor. Essential epilepsy in such rare cases may be independent of the intracranial pressure and may be caused by the particular biocerebropathic conditions created by the tumor and of themselves sufficient to cause epilepsy. The facts that in the author's case the acromegaly became evident before the development of the tumor of the brain and that the hypophysis was found to be normal indicate that the acromegaly had no causal relationship to the tumor, and that an anatomic or neoplastic lesion of the hypophysis is not a necessary condition for the development of acromegaly. The author believes that the acromegaly in his case was due to the metaplastic anterior hyperpituitarism consecutive to the spreading of the inflammatory meningeal process localized particularly in the anterior cranial fossa. The coexistence of the tumor of the brain with the chronic meningitis and the acromegaly suggests that in the pathogenesis of tumors of the brain several factors concur, in particular, the neurohormonal factor as the cause of a disorderly and atypical development of tissues, and an irritative factor acting as a local stimulus for the active proliferation of the tissues.

YAKOVLEV, Palmer, Mass. [ARCH. NEUROL. & PSYCHIAT.]

A CONTRIBUTION TO THE PROBLEM OF CHOREA MINOR: II. TREATMENT. G. LENART and E. VON LEDERER, Arch. f. Kinderh. **95**:11 (Nov. 30) 1931.

The authors believe that phenyl-ethyl-hydantoin, a urea derivative, is of distinct advantage in shortening the course of chorea minor and lessening the complications. The urea derivative was given in daily doses of 0.15 Gm. until the appearance of the phenyl-ethyl-hydantoin exanthem. If the exanthem did not appear within twelve days, the drug was discontinued at this time. From three to five days after they began to receive the drug, the patients showed clinical improvement. Usually on the tenth day a measles-like eruption appeared with more or less itching, a moderate fever and an eosinophilia. In three or four weeks the patients were completely well.

The authors do not make clear the relationship between the treatment of chorea minor with phenyl-ethyl-hydantoin and the lowered secretion of the parathyroid glands. In their first paper they had suggested that these parathyroid glands were etiologic factors in chorea minor.

LESLIE, Evanston, Ill.

HEMIATROPHIA LINGUAE. H. PAAL, Deutsches Arch. f. klin. Med. **172**:335, 1932.

The author reports three cases of hemiatrophy of the tongue consequent to unilateral, peripheral involvement of the nervus hypoglossus, rami linguales. The ramus descendens and ramus thyreohyoideus were spared. The atrophy affected the fore part of the tongue chiefly, and was not associated with subjective symptoms. Excitability, as evidenced by the reaction of degeneration, was reduced considerably in one case, but only slightly in the other two. Taste was affected in about the same degree.

DOOLEY, Kent, Conn.

PRESENT-DAY CHILD PSYCHOLOGY AND THE PEDIATRICIAN. C. BÜHLER, Kinderärztl. Praxis **2**:434 (Oct.) 1931.

The interpretation of the same symptom in the same child may vary according to his developmental age. For instance, lying before the age of puberty may be associated with beginning sexual development or due to fantasies common at that period of life, while lying after puberty usually points to a defect of character. The most recent researches in child psychology have been in the field of social development, i. e., the child's relations with other people, rather than in skill with things, as in the various intelligence tests. As early as the second year of life, the author has been able to demonstrate fundamental differences in the reactions of children to one another in given play situations.

HUENEKENS, Minneapolis.

THE RESULTS AND LIMITATIONS OF THE MEDICINAL TREATMENT OF EPILEPSY. K. HENNER, Časop. lék. česk. **69**:425 (March 14); 463 (March 21); 503 (March 28); 536 (April 4); 575 (April 11); 611 (April 18) 1930.

The author reviews the treatment of sixty-eight patients with a résumé of each case. The discussion includes the history, diet, hygiene, medication and general care. These patients were under observation for periods as long as six and three-quarters years. Of this group twenty-three made clinical recoveries, and fifty-five were improved. The important drugs, according to the author, are bromides, phenobarbital and sodium or potassium tartarico-boraxatum. Alcohol is absolutely contraindicated, as some of the patients had convulsions after merely applying alcohol to the face as a lotion. Small quantities of coffee are permissible. A rational hygienic regimen is of definite value. Diurnal sleeping is usually discouraged because of the observation of increased convulsions in patients accustomed to sleep during the day.

STULIK, Chicago.

CONVALESCENT SERUM FOR POLIOMYELITIS. A. PONDMAN, Nederl. tijdschr. v. geneesk. **75**:5986 (Dec. 12) 1931.

The author first explains how the therapeutic value of convalescent serum in poliomyelitis was established. He then criticizes some statistical facts and judgments based on the practical application of this serum. The conclusion is drawn that the results reported are rather satisfactory. The preparation, application, place of injection and amount of serum to be given are discussed. The measures taken in Holland and in Canada with regard to the possibility of treatment with the serum on a large scale are compared. The State Serologic Institute of Holland has formed a center for this convalescent serum and the author recommends that the same action be taken for other convalescent serums.

VAN CREVELD, Amsterdam, Holland.

SEROUS MENINGITIS. D. HERDERSCHÊE, Nederl. tijdschr. v. geneesk. **75**:6079 (Dec. 19) 1931.

In this article are discussed the acute diseases characterized by symptoms of meningitis in which by lumbar puncture a clear fluid under high pressure

and showing an abnormal protein content and cell count is obtained. The author arrives at the following conclusions:

1. As soon as symptoms of meningeal irritation are observed, lumbar puncture should be done, not only for the determination of the prognosis (tuberculosis), but especially as a means of treatment (in syphilis, poliomyelitis and epidemic meningitis).

2. If by lumbar puncture the fluid is found to be cloudy, the needle should not be taken away before the sugar concentration has been determined (Fehling's reaction). If the concentration is too low, antimeningococcal serum should be given; if the concentration is too high or normal, poliomyelitis reconvalescent serum should be administered.

3. If the fluid obtained by lumbar puncture is clear, the reaction of Pandy (8 per cent) decides between the diagnoses of meningism and serous meningitis. A normal or too high sugar concentration makes it necessary to make a choice between encephalitis and poliomyelitis.

4. There is no meningitis serosa *sui generis*.

VAN CREVELD, Amsterdam, Holland.

WOUNDING OF THE DURAL SAC. M. WEERSMA, Nederl. tijdschr. v. geneesk. **75**:6089 (Dec. 19) 1931.

The author describes a case of lumbar fistula, in a boy of 8 years, caused by a dural wound after a knife thrust. There was no injury to the nerve substance. Quick subsidence of meningitic symptoms took place after an injection of acriflavine into the cisterna. Spontaneous closure of the fistula occurred eleven days after trauma. On the basis of this and other personal observations and of those of other authors, Weersma suggests the use of intradural injections of acriflavine in all cases in which infection of the cerebrospinal fluid exists. In cases that resemble the one reported surgical intervention in his opinion need not be resorted to too quickly.

VAN CREVELD, Amsterdam, Holland.

Diseases of the Eye

OPHTHALMIA NEONATORUM. M. S. MAYOU, Brit. M. J. **2**:973 (Nov. 28) 1931.

Ophthalmia is considered bacteriologically from the standpoint of various causes, and the term is not limited in this article to gonorrheal infection, though this infection is stressed. Complications and treatment are also discussed.

ROYSTER, University, Va.

TWO CASES OF PALPEBRAL GRANULOMA. A. RIFAT, Ann. d'ocul. **169**:198 (March) 1932.

In two cases, one in a boy of 15 years, and the other in his cousin, aged 10, the symptoms and course were identical. In the first patient there were multiple tumors, and three of the eyelids as well as the cheeks were affected. The duration of the disease was eight years for the right and seven years for the left eye. In the second case, only one lid was affected, and the duration was five years. The tumors developed slowly and without any acute inflammatory reaction. These subjects did not show any signs of syphilis or tuberculosis, or any other infection clinically. The lymphatic glands were normal. In the first case there were blood changes of moderate degree in the white and red cells, in their number and in their biologic properties. The number of white cells slowly increased, while the polymorphonuclears and eosinophils were little different from normal. There was marked anemia—3,000,000 red cells with parallel diminution of hemoglobin. In the second case the white cells were only slightly increased.

At operation encysted tumors were found forming white masses and enclosing numerous nodules of different sizes. They were adherent to the skin at different points, and in the first case there was extension from the inferior lid to the orbit. The tumors were formed of lymphocytes, plasmocytes and large cells of clear photoplasm and inflammatory conjunctival element. These cases differ from those that McAll observed in central China. In the latter the subconjunctival granuloma generally settled near the internal canthi, the masses developed in front of the globe and made deep cavities in the lids resembling the conjunctival culdesac, and the lids progressively increased in size until there was mechanical occlusion of the palpebral fissure.

It is impossible to establish the nature of these lesions, which are probably infectious.

McKee, Montreal, Canada. [Arch. Ophth.]

Interstitial Keratitis in the Infant. Mario Tejeda Lawrence, Rev. chilena de pediat. **3**:122 (March) 1932.

The author reports a case of congenital syphilis with most of the severe and acute symptoms of the disease in a 2 month old infant. The Wassermann reaction of the infant, as well as of both parents, was 4 plus. In addition, the child presented a most unusual manifestation at this age, namely, a total opacity of the right cornea which completely occluded the pupil.

In view of the symptoms and laboratory findings of severe, acutely manifested syphilis, a diagnosis of parenchymatous or interstitial keratitis was made.

The child died a month later. Autopsy revealed severe septicemia.

The ocular condition, however, had improved somewhat under specific treatment. The author presents a differential diagnosis of the ocular manifestation and states that this is the only case of syphilitic keratitis in an infant reported in the Chilean literature.

Schlutz, Chicago.

The Genesis of Congenital Opacities of the Lens. A. Loewenstein, Klin. Monatsbl. f. Augenh. **87**:382 (Sept.) 1931.

The examination of six new patients prompts the author to the opinion that inflamed filaments of the pupillary membrane pierce the capsule of the lens, causing disturbances in its development in the shape of a congenital cataract, or a spot in the capsule, or a subcapsular shell, but most frequently in the shape of a spindle or zonular formation. The pigment in the bag of the capsule, visible as a filament on the apex of a spindle-shaped cataract, is derived from these remnants of the pupillary membrane. Inflammatory adhesions frequently prevent the physiologic disappearance of the pupillary membrane, filaments of which, on the other hand, may disappear even in adults. Typical heaped remnants of posterior synechiae in young persons may be transformed into the star-shaped, so-called congenital pigmentation of the capsule of the lens. Star-shaped pigment needles, therefore, should be considered as inflammatory products of the uvea.

Stoll, Cincinnati. [Arch. Ophth.]

Diseases of the Ear, Nose and Throat

Lung Abscess Following Tonsillectomy. Joseph S. Wall, Arch. Pediat. **48**:687 (Nov.) 1931.

The author speculates concerning the "remarkable circumstance that lung abscesses following tonsillectomy have been recognized only during less than a score of years." The incidence of pulmonary abscess from this cause is discussed, and the various theories concerning the etiology of such abscesses are presented. The symptomatology, diagnosis, prognosis and treatment are discussed.

Waddell, University, Va.

THE HARD OF HEARING SCHOOL CHILD. ROBERT M. TAYLOR, Laryngoscope **41**:753 (Nov.) 1931.

Since the introduction of the audiometer as a means of testing the hearing in large numbers of school children, it has been possible to detect many instances of hearing defects in those who formerly had been considered to hear normally. Large numbers of children, both in elementary and in high schools, are hard of hearing to an extent that handicaps their progress. It is estimated that there are over 3,000,000 school children in this country with some defect in hearing, in more than 340,000 of these the hearing being impaired to such an extent as to require special training in lip-reading. The author makes an urgent plea for the careful examination of all school children with the audiometer, the classifying of those with hearing defects into various groups according to the degree of defect and the giving of proper special training to these various groups. An audiometric loss of from 9 to 12 per cent calls only for special attention by the teacher, such as a quiet classroom and a front seat; a loss of from 12 to 15 per cent calls for regular lip-reading class work two or three times a week, superimposed on the regular class work; those with a loss of from 15 to 20 per cent require special training, and those with a hearing loss of more than 25 per cent should be segregated in oral schools for the deaf. Even the last group of pupils have speech, but tend toward errors of enunciation.

The inefficient organization of hospital outpatient clinics and the incompetent medical care rendered in these clinics are pointed out by the author. The men doing this work are not paid for their services, the physician usually holding the position on the outpatient staff simply for the purpose of keeping in line for a regular staff appointment or in order to train himself in the work. Patients with chronic conditions drag along month after month, and finally get tired because of lack of results and go to another clinic for a repetition of the same thing. A plea is made for the compensation of the physician doing this work, as well as for the provision of a competent otologist as chief to direct the work of those on service in the clinic. More careful attention to the individual case in the clinic would result in marked conservation of hearing in large numbers of school children.

SNAPP, Grand Rapids, Mich. [ARCH. OTOLARYNG.]

AN ASCARIS IN THE MASTOID PROCESS. K. B. STEINMAN, Rev. med. de Chile **59**:167 (Feb.) 1931.

In an 8 year old girl an ascaris was removed from the right mastoid process during an operation for acute mastoiditis which followed an attack of scarlet fever. The symptoms appeared three days before the operation. The parasite was alive when found and was properly identified at the zoological laboratory. The three possible modes of entrance are: (1) the external acoustic meatus, (2) the blood stream (hematogenous) in a microscopic stage and (3) the eustachian tube (this seems to be the most probable one).

SCHLUTZ, Chicago.

EPIDEMIC SEPTIC PHARYNGITIS WITH SEVERE ENTERITIS. B. EXNER and H. KOTRNETZ, Jahrb. f. Kinderh. **132**:169 (July) 1931.

An epidemic of forty cases of pharyngitis with acute enteritis and pneumonia due to the hemolytic streptococcus is described. Favorable results are ascribed to polyvalent autogenous vaccines and antistreptococcus serum.

CLAUSEN, Rochester, N. Y.

RULES FOR OPERATIVE TREATMENT IN ATRESIA OF THE NOSTRILS. D. N. MATWEJEW, Monatschr. f. Ohrenh. **65**:1188 (Oct.) 1931.

After calling attention to the disorders that may result from atresia of the nostrils, Matwejew enumerates the conditions that may cause atresia, such as

smallpox, diphtheria, scarlet fever, eczema, lupus, tuberculosis, syphilis and all conditions in which ulceration of the nasal mucous membrane exists. In rare instances the atresia is congenital. The author considers smallpox one of the most frequent causes of atresia, for all of the cases that were treated by him were caused by it. The pustules at the entrance of the nose cause cicatricial contraction of the nostrils or even complete closure, and the cicatricial changes in the skin around the nostrils constitute a great difficulty in the plastic correction of atresia, for the condition usually returns. To avoid a relapse, the author suggests the following rules for the operative treatment: 1. In the area of the operative field the epitheliated cutaneous covering should be preserved even where it is cicatrized. 2. In order to avoid the contraction of the cutaneous covering, the subcutaneous cicatricial strands should be removed. 3. All wound surfaces produced by the surgical intervention should be covered with epitheliated skin. After giving a detailed description of his operative technic, the author expresses the hope that his method will be employed by others.

EDITOR'S ABSTRACT. [ARCH. OTOLARYNG.]

ANATOMY OF DEAFNESS RESULTING FROM CEREBROSPINAL MENINGITIS: HISTOLOGIC ASPECTS OF CHRONIC LATENT OTITIS INTERNA. K. ISHIHARA, Monatschr. f. Ohrenh. **65**:1199 (Oct.) 1931.

Because the literature on the histologic aspects of postmeningitic deafness is limited, Ishihara feels justified in reporting a case which, for a number of years, had been under clinical observation and in which the postmortem examination revealed noteworthy histologic aspects. The meningitis developed in January, 1915, when the girl was in her fourth year. Deafness set in on the fourth day of the meningitis, but neither vertigo nor nystagmus was observed, and the author thinks that this is due to the fact that deafness and the exclusion of the labyrinthine function developed on both sides simultaneously. In her sixteenth and seventeenth year, the patient complained of attacks of dizziness before and after menstruation, but it is not likely that these attacks were of labyrinthine origin, for repeated clinical tests revealed the labyrinths as unexcitable. However, it is pointed out that even thirteen years after the beginning of the labyrinthine disease (the patient died in 1928, in her seventeenth year), there was a remnant of the labyrinthine neuroepithelium, and it was connected with the nerve, which was atrophied to a considerable degree. Thus the histologic aspects of the right ear indicate the possibility of a slight labyrinthine vertigo. The attack of unconsciousness, which the patient experienced during 1927, is ascribed to the congenital narrowness of the vascular system, and it is assumed that such an attack was the cause of the patient's sudden death. The author describes the results of the necropsy and of the histologic examination of both ears. The latter corresponds with the results of the functional tests, which indicated bilateral deafness and loss of the labyrinthine function. However, it seems surprising that, although the deafness developed simultaneously on both sides and was caused by the same disease, the histologic changes in the two ears show considerable differences. The author describes numerous sections of both ears and also summarizes the differences in the histologic aspects. As one of the differences, he points out that whereas in the left ear the inflammation of the internal ear had completely healed, in the right ear there still were signs of inflammation. However, some of the changes are the same in both ears.

EDITOR'S ABSTRACT. [ARCH. OTOLARYNG.]

TECHNIC OF TONSILLECTOMY OF CHILDREN. P. OHNACKER, Ztschr. f. Hals-, Nasen- u. Ohrenh. **30**:94 (Oct.) 1931.

Ohnacker describes his modification of Sluder's method and then emphasizes two factors that are of special significance in children, namely, the behavior of the veins and the softness of the tonsils. The veins in the tonsillar bed are comparatively stronger in children than in adults, and are injured more easily; how-

ever, this is no cause for alarm, for a clamp will suffice to check the hemorrhage. Because of the softness of the infantile tonsils, special care has to be taken so that the grasping forceps do not slip. EDITOR'S ABSTRACT. [ARCH. OTOLARYNG.]

A CASE OF DIFFUSE, ACUTE, OTOGENIC OSTEOMYELITIS OF BOTH TEMPORAL BONES. J. ALPIN, Ztschr. f. Hals-, Nasen- u. Ohrenh. **30**:105 (Oct.) 1931.

Alpin gives the clinical history of a boy, aged 13 years, in whom the clinical picture, the operative status and the postoperative course indicated the presence of fulminating, septic otogenic osteomyelitis of both temporal bones. The patient recovered because a wide resection of the bone checked the further spreading of the process and because an intracranial complication (sinus thrombosis) was removed. The reported case is of special interest for the following reasons: its great rarity, favorable outcome and relapse-free course during a period of two years and the complete epidermization of the large trephined cavities. Since the patient had a normal hearing capacity before, a bilateral infectious toxic neuritis of the cochlear nerve is assumed.

EDITOR'S ABSTRACT. [ARCH. OTOLARYNG.]

Diseases of the Skin

THALLIUM ACETATE IN THE TREATMENT OF RINGWORM OF THE SCALP. JOHN T. INGRAM, Brit. M. J. **1**:9 (Jan. 2) 1932.

In this paper, the author discusses the relative values of thallium acetate and of the roentgen rays in the treatment for tinea capitis, and concludes, from a study of the literature, that the dermatologists with the greatest experience in the use of thallium are favorably disposed toward its use, while those who condemn it do so from a limited acquaintance. He has treated 101 patients with thallium acetate, 94 successfully, and feels that the more the drug is used, the less apparent is the danger. Thallium is a heavy metal with toxic properties and, of course, cannot be used indiscriminately. Instances of death following the use of the drug have all been from accidental overdosage or from repeated large doses. Toxic reactions are usually unimportant, and even when very severe, the patient always recovers. There is no serious evidence in the literature to support the suggestion that the treatment may do permanent damage to the growing organism. Ingram's procedure is to weigh the child naked, and the weight in pounds multiplied by 4 gives the required dose of thallium acetate in milligrams. If the dose is under 200 mg., the patient may be treated as an ordinary outpatient; if the dose is between 200 and 250 mg., the child should be kept under observation, and if between 250 and 300 mg., the patient must be treated in bed. More than 300 mg. of the drug is never administered. In the event that treatment must be repeated, there should elapse an interval of not less than three months. Locally, every day from the onset of treatment, the entire scalp is to be painted three times a day with 2 per cent tincture of iodine, and the scalp is not to be washed during the first two weeks. Ingram has found this procedure perfectly safe, and the results have been satisfactory.

RATTNER, Chicago. [ARCH. DERMAT. & SYPH.]

A SPECIAL FORM OF LUPUS ANNULARE, WITH A PERIFOLLICULAR HISTOLOGIC STRUCTURE. JEAN PIERARD, Ann. de dermat. et syph. **2**:877 (Aug.) 1931.

The author reports a case of undoubted tuberculosis of the skin, apparently a transition form between lupus vulgaris and certain tuberculids, but difficult to classify. The patient was a lad of 6 years, and the lesion, situated in the right temporal region just above the zygomatic arch, was of nine months' duration. It consisted of a coin-sized ring of papular elements covered with fine pearly scales, the lesion as a whole showing peripheral extension and central involution, with scar formation. The clinical resemblance to epithelioma was marked, but removal of

the scales revealed a reddish, irregular, papular border which exhibited translucent apple jelly nodules under pressure of the diascope. The microscopic picture was definitely that of lupus vulgaris, the striking feature being the disposition of the infiltrate about the pilosebaceous structures.

The differential diagnosis is discussed, both clinically and histologically, between the various forms of tuberculosis that one would have to consider in this case, such as circinate lupus erythematosus, Boeck's sarcoid, lichen scrofulosorum and papulonecrotic tuberculids, with the conclusion that it best fits into the category of Brocq's "lupus annulare," representing, however, a peculiar variety of this condition by reason of the perifollicular arrangement of the tuberculous infiltrate.

GANDY, Houston, Texas. [ARCH. DERMAT. & SYPH.]

THALLIUM ACETATE IN THE TREATMENT FOR RINGWORM. A. MARTINS DE CASTRO, Ann. de dermat. et syph. **2**:1056 (Oct.) 1931.

An experience with fourteen cases of ringworm and favus in which thallium acetate was employed to produce alopecia of the scalp convinces the author that the prejudice that has grown up against the use of this drug, owing to the many reported toxic reactions of one kind or another, is not justified. By using it only before puberty, in proper dosage (8 mg. per kilogram of body weight), and carefully examining the patient before to make sure that all organs were sound, he found the reactions to be of small moment, and obtained perfect therapeutic results. In areas that are inaccessible to the roentgen rays, or when the patient is too young, thallium should be employed.

GANDY, Houston, Texas. [ARCH. DERMAT. & SYPH.]

A CASE OF CHRONIC URTICARIA AND EDEMA OF FUINCKE. P. NOBÉCOURT, Progres méd., Feb. 13, 1932, p. 282.

The author presents the case of an 8 year old girl who had had chronic urticaria and edema since she was 9 months old. The etiology was uncertain.

SANFORD, Chicago.

ROENTGEN DEPILATION IN THE TREATMENT OF RINGWORM. OSCAR SOTO and HUGO PESCE, Arch. de pediat. d. Uruguay **2**:209 (May) 1931.

The authors conclude that superficial roentgentherapy fulfils completely all dermatologic indications for temporal depilation in the treatment of ringworm in children. Temporal roentgen depilation constitutes a rapid, painless and aseptic method, the effect of which is both radical and esthetic if the method is carefully carried out with an adequate technic that guards against all danger of producing permanent alopecia. It is perfectly harmless and will give exceptionally fine results.

The authors have not seen an unfavorable result in a single instance.

SCHLUTZ, Chicago.

XANTHOCHROMIA OF THE PALMS AND SOLES. F. NICOLA REYES and W. AYALA, Arch. de pediat. d. Uruguay **2**:538 (Nov.) 1931.

This condition occurred in a boy of 8 years in whom there was an acute pulmonary process accompanied by coughing, vomiting and high fever. He presented intense yellow staining on the palms and the soles. The rest of the skin was less yellow. The conjunctivae were not discolored. The mucous membranes showed slight discoloration. The liver was large. The urine contained no pigment, but showed a slight reaction to acetone. The tuberculin and Wassermann tests gave negative reactions.

The author believes that the condition was due to the consumption of a native herb (Coronopus diynamus—Mastuerzo-Hembra) which is used by the natives as an infusion. The fruit of this herb contains intense yellow pigment.

SCHLUTZ, Chicago.

DERMATOMYCOSIS CAUSED BY THE "TORULA EPIZOA CORDA." A. P. ALATORZEFF, Arch. f. Dermat. u. Syph. **164**:279, 1931.

In two cases of tinea of the scalp in children caused by Trichophyton tonsurans-violaceum, there were in addition to the usual patches a few flat, hard, millet-sized nodules scattered over the head. From the latter areas an organism called "Torula epizoa corda" was isolated. The same organism was also found in several dogs showing a nodular eruption. By rubbing a culture into the skin of dogs, the author was able to produce a nodular eruption, and he demonstrated the presence of the spores in the upper layers of the affected skin.

MONASH, New York. [ARCH. DERMAT. & SYPH.]

ATYPICAL TINEA ERUPTIONS. AUGUST MATRAS, Arch. f. Dermat. u. Syph. **164**:291, 1931.

In two cases showing a generalized exanthem together with typical tinea infection of the feet, caused by the Kaufmann-Wolf organism, the reactions to trichophytin (Hoechst 1:50) were negative. The author, basing his conclusion on the work of Naegeli on allergic conditions in syphilis and tuberculosis, considers the absence of an allergic reaction in these cases to be due to an overwhelming of the antibodies by an excess of antigen.

Matras in addition describes two cases in which lesions resembling tinea circinata were present on the thighs and trunk. The causative organism was found to be the Epidermophyton inguinale, although the groin was free from lesions.

MONASH, New York. [ARCH. DERMAT. & SYPH.]

A CASE OF HEMANGIOMA CAPILLARE SIMPLEX. KURT OCHSENIUS, Jahrb. f. Kinderh. **133**:326 (Nov.) 1931.

Most textbooks of pediatrics fail to mention hemangiomas. In the present case, the tumors appeared on the seventh day of life: 189 were present at 2 months of age. Excision was followed by some local recurrence, but no new tumors had appeared at 4 months.

CLAUSEN, Rochester, N. Y.

TUBERCULOSIS CUTIS MILIARIS ACUTA GENERALISATA IN CHILDHOOD. E. NEDELMANN, Jahrb. f. Kinderh. **134**:24 (Dec.) 1931.

After measles, in a child, aged 3 years, a high continued fever developed and finally enlargement of the spleen and of the liver and a generalized rash. In certain individual lesions small necrotic centers developed; otherwise the lesions did not resemble papulonecrotic tuberculids. The intradermal reaction to tuberculin repeatedly was negative. Histologic study of the lesions revealed acid-fast bacilli but no specific tuberculous reaction.

CLAUSEN, Rochester, N. Y.

Surgery and Orthopedics

STABILIZATION OF THE FOOT; A STUDY OF LATE RESULTS. L. J. MILTNER, J. Bone & Joint Surg. **13**:502 (July) 1931.

The results of the various stabilizing operations on the foot, as seen in the clinic of Dr. Steindler, are reported. Satisfactory results were obtained in 85 per cent of the cases in the series. The etiology of diseases necessitating surgical intervention comprises infantile paralysis, fracture of the astragalus, tuberculosis

of the ankle, congenital clubfoot, spastic hemiplegia, congenital contractures, progressive muscular dystrophy, spina bifida, chronic infectious arthritis, posttraumatic arthritis and chronic osteomyelitis.

The operations practiced include astragalotarsal stabilization, tendon transplants and panastragaloid arthrodesis. Tables are given showing the results of each type of operation and disease treated.

Of particular interest to the pediatrician are the tables of statistics, especially the columns detailing the percentage of patients in whom pain was still complained of postoperatively.

RYAN, Vancouver, B. C.

THE DIAGNOSIS AND TREATMENT OF ACUTE OSTEOMYELITIS IN CHILDHOOD. G. C. PENBERTHY, J. Michigan M. Soc. **30**:474 (June) 1931.

Penberthy gives an adequate short review of the etiology, pathology, diagnosis and treatment of osteomyelitis. He believes that trauma is an important etiologic factor, that the infection is blood borne and that the process is thrombo-embolic.

SMITH, Ann Arbor, Mich.

PAINFUL SPINA BIFIDA OCCULTA (LUMBAR) CURED BY LAMINECTOMY. E. ESTOR and H. ESTOR, Rev. d'orthop. **18**:664 (Nov.) 1931.

Spina bifida occulta, a more rudimentary form of spina bifida characterized by a loss of the posterior part of the vertebral arcs, is seen more and more frequently since the excellence of roentgenograms has improved. The symptomatology and associated malformations have often been described, but the sensory disturbances, which may be so pronounced as almost to make a special classification —a "painful form"—seem to have been neglected. Several authors have drawn attention to this form and have reported cures following laminectomy. The Estors report their observations in one case: a lack of development of the fifth lumbar arch in which relief from symptoms followed removal of the rudimentary laminae. This case had been erroneously diagnosed as Pott's disease, but the roentgenogram demonstrated a loss in the arch. It is therefore essential that good roentgenograms be made in every case, since spina bifida occulta may coexist with Pott's disease. Treatment depends on the type of lesion present; in the less marked "painful form" roentgen therapy alone may produce relief. The severer forms need laminectomy to remove the pressure from the bulging sack, accompanied by removal of the fibrous bands strangling the end fibers of the cord. This operation is often followed by rapid and definitely favorable results.

RYAN, Vancouver, B. C.

OSTEOMYELITIS OF THE SUPERIOR MAXILLARY IN THE INFANT. JUAN CARLOS OREGGIA and EDUARDO PALMA, Arch. de pediat. d. Uruguay **2**:430 (Sept.) 1931.

The case reported occurred in an infant boy of 27 days. Purulent right-sided coryza developed on the sixth day, and then a swelling appeared in the right suborbital angle. This opened spontaneously, and discharged pus. Staphylococcic and pneumococcic organisms were found in the cultures. A large part of the external wall of the nasal fossa was destroyed. Incision and drainage caused a complete cure.

SCHLUTZ, Chicago.

OPERATION FOR CLEFT PALATE. HANS KINZEL, Beitr. z. klin. Chir. **152**:618, 1931.

After operating on 234 patients, the author came to the conclusion that though the total mortality is 3.8 per cent, between the ages of 1 and 3 years, the mortality is 15 per cent. The best cosmetic results are obtained in later years. From 1 to 3 years of age, complete cure is obtained in 34.3 per cent of the cases;

from 4 to 6 years of age, in 40.6 per cent; from 7 to 14 years of age, in 42.8 per cent, and from 14 years of age up, in 57 per cent. One must also take into account the seasonal variation. The best results are obtained between May and September.

Whereas complete closure and cure were obtained in 107 cases, or 45.6 per cent, and improvement in 83 cases, or 37.3 per cent, total improvement in speech was found in only 10 per cent of the cases, while some improvement was found in 68 per cent and no improvement in 25 per cent, even though there was thorough cooperation with other clinics. This discouraging factor may be due either to an insufficient length of the soft palate or to the inability of the soft palate to contract.

RUBIN, Boston.

CYSTIC LYMPHANGIOMA OF THE NECK. G. BOLINTINEANO and G. BAJEU, Spitalul **52**:26 (Jan.) 1932.

After a review of the etiology and pathologic anatomy of serous lymphangiomatous cysts of the neck, an interesting observation of a tumor of this sort in a girl of 14 years is reported.

AUTHORS' SUMMARY.

Miscellaneous

REPORT ON THE SERVICE OF DEPENDENT CHILDREN OF THE DEPARTMENT OF THE SEINE (FRANCE) DURING THE YEAR 1930. Director General of the Administration of Public Assistance.

The report is issued in two sections, the second of which contains the financial report. The first section has to do with the various phases which constitute the help and supervision rendered by the department in the year 1930 to the children dependent on it. These phases include measures taken to lessen the abandonment of children, care and supervision of infants and children in institutions and foster homes, preventive medical measures, hospital care, provisions for the schooling of older children and efforts to establish them in life as normal citizens.

In addition to the official report the administration has issued a booklet for the layman, which gives an idea of the scope, problems and aims of the work; a second book describing the facilities offered by the department to those wishing children for adoption has also been issued.

LESLIE, Evanston, Ill.

THE DEVELOPMENT OF SCHOOL HYGIENE IN ITALY. M. RAGAZZI, Rev. internat. d. l'enf. **12**:132 (Sept.-Oct.) 1931.

In certain communities in Italy, medical inspection of school children has been practiced for a century; the Public Health Act of 1888, however, made this service compulsory in the entire school system of that country. Based primarily on the need for control of communicable disease among the children, the work has grown until it now embraces the comprehensive hygiene of school buldings, the utilization of school nurses, the correction of remedial defects and the organization of open air schools and seaside camps. There are special schools for the mentally abnormal and for vocational guidance; through the magazine, *School Health*, school physicians are kept in contact with each other and with the central bureau.

AMESSE, Denver.

Society Transactions

CHICAGO PEDIATRIC SOCIETY

Regular Meeting, Oct. 18, 1932

ARCHIBALD HOYNE, M.D., *President, in the Chair*

TREATMENT OF CONGENITAL SYPHILIS WITH ACETARSONE (STOVARSOL) BY MOUTH. DR. ALFRED S. TRAISMAN.

Acetarsone (stovarsol) is a preparation containing from 27.1 to 27.4 per cent arsenic. This preparation administered by mouth was used in the treatment of fifty-four patients with congenital syphilis. The following method of dosage was used in this series: The first week, 0.005 Gm. per kilogram of body weight was administered daily; the second week, 0.010 Gm.; the third week, 0.015 Gm.; the fourth week, 0.020 Gm. For the following five weeks, the dosage was 0.020 Gm. per kilogram of body weight daily.

The total duration of the course of treatment is nine weeks. A rest period of six weeks follows the treatment. The drug is administered by mouth. The amount ordered is dissolved in water and given one-half hour before feedings.

In the group of infants under 1 year of age 71 per cent of the patients showed a reversal of the Wassermann and Kahn reactions. In the group of children between the ages of 1 and 6 years, the Wassermann reaction became negative in 55 per cent of the cases, and the Kahn reaction became negative in 33 per cent of the cases. In the group between 6 and 12 years of age, the Wassermann reaction became negative in 47 per cent, and the Kahn reaction became negative in 19 per cent of the cases.

Of the forty patients who completed a second course of acetarsone therapy, the Wassermann reaction became negative in 50 per cent and the Kahn reaction in 33 per cent. The clinical symptoms improved rapidly, and the physical development also showed marked improvement. No serious urinary changes were noted in this series, except in one child who had a severe arsenical dermatitis. The blood of the younger infants showing a secondary anemia improved rapidly with acetarsone treatment. Eosinophilia was a frequent observation. Lesions of the bones healed rapidly in all cases after one course of treatment, both clinically and according to the roentgenograms.

The untoward reactions were few and very slight in this series, with the exception of that of one child in whom a severe arsenical dermatitis developed, and who expired on the seventeenth day after the onset of symptoms.

Examinations of the spinal fluid gave negative results in the thirty-one cases in which such an examination was made.

The results obtained in this series of cases warrant the belief that the peroral administration of acetarsone in the treatment of congenital syphilis is the method of choice. The cooperation of the parents and children was greatly increased because this method of treatment was used. Little difficulty was encountered in having the children return regularly for the medication.

It should be strongly emphasized that patients being treated with acetarsone should be kept under careful and close observation. Parents should be warned that at the first sign of fever, vomiting, or diarrhea or the appearance of a rash, the medication should immediately be discontinued. In this manner, any serious untoward effects can be eliminated.

DISCUSSION

DR. HENRY E. IRISH: I feel that this paper advocating a method of administration somewhat different from the one now accepted by most physicians should have some discussion.

In Tice's "Practice of Medicine" there is an article by Stokes of Philadelphia on syphilis in children. To me that article is well worth while, as the statements he makes coincide with my own clinical experience. He says that in the treatment of syphilis in infants rest periods should not be given. His plan regarding the use of different drugs (arsenic and bismuth) and the reasons he gives for changing them are founded on an experience so wide that it embraces almost all the occasional mishaps that occur in the treatment of syphilis in infants. I think that it is true that almost any treatment is successful, and yet as one's experience grows one becomes convinced that the former treatment, which consisted largely of the administration of mercurials, did not prevent the terrible conditions that occur in later life and some of the conditions that occur in early life. For instance, under that treatment I have seen two cases of hemorrhagic pachymeningitis, one fatal and one resulting in hemiplegia.

While I was listening to this paper the thought came to me that a treatment of this kind, which in many ways is similar to the mercurial treatment, with which the older physicians are familiar, and which will be administered largely by the family in the home, presents variabilities that are quite likely to result in failure to secure the best results. I feel that the cases in which I obtain the best results are those in which the hypodermic administration of the drug is employed. I feel that there is something in the exactness of the dosage and time of administration that is well worth while. While I think this study is excellent in its scope and in the presentation of an alternative plan of administration, I feel sure that at present I would much prefer to continue hypodermic medication than to resort to the oral method.

A CLINICAL STUDY OF EPIDEMIC POLIOMYELITIS. DR. LUKE W. HUNT (by invitation).

The initial symptoms in 368 cases of epidemic poliomyelitis of the dromedary type and of the struggling type assumed three main characteristics: gastrointestinal, tonsillar and upper respiratory inflammation and malaise, without the localization of symptoms. In the group in which the onset was sudden, the symptoms point from the start to meningeal involvement and to involvement of the nervous system. Fever occurred in 306 of the 368 cases, nausea and vomiting in 205, abdominal pain in 30, diarrhea in 18 and constipation in 32. Seventy-two of the 368 patients showed symptoms of involvement of the upper respiratory tract. There was a history of headache in 137 patients and pains in the back or extremities in 103. Convulsions occurred in 8, delirium in 3, coma in 1.

Partial paralysis was more common than total paralysis, the former occurring in 246, or 67.9 per cent, of the 362 cases. Paralysis of the muscles of the legs was more frequent than paralysis of the muscles of the arms. The muscles of the upper extremity were more severely affected nearest the trunk; in the leg the largest proportion of severe paralysis was in the lower part of the leg and the foot.

Of the 368 patients 212, or 57 per cent, were children 4 years of age and under. The death rate for the series was 8.9 per cent. The greatest percentage of deaths occurred in the age group from 10 to 19. The greatest relative percentage of deaths occurred early in the season, which seems to indicate that the early cases are the most severe. Eleven cases occurred in Negroes, 357 in white persons. The type of child most susceptible to the disease was the large, well developed, plump child.

Of the 326 patients whose spinal fluid was examined, 201 showed cell counts of from 0 to 100; 80 had from 100 to 200 cells; 45 had 200 or more. Six patients

had cell counts of 1,000 or more. In the fatal cases the cell count was invariably high, the average being 200 or more. Globulin was present in 290 of the cases.

Autopsy performed in 13 of the 33 fatal cases showed hyperemia, edema, dilatation of blood vessels, slight hemorrhages and a perivascular infiltration of round cells. The ganglion cells were swollen and showed chromatolysis with disintegration. Other changes were hyperplasia of the lymphatic glands and spleen and cloudy swelling of the organs.

The majority of the patients were admitted after the paralysis had developed. Convalescent serum was used in a small percentage of cases, but no conclusions can be drawn as to its value in this group. In some cases there was marked improvement after its use. The care in the acute stage of the disease and during the three to five weeks of required isolation consisted for the most part in immobilization of the affected parts in the proper position by splints made of one-fourth inch mesh wire and properly padded or occasionally by casts, plenty of food and fluids, careful attention to elimination, warm baths and care to make the patient as comfortable as possible and to prevent bed sores.

ACUTE ANTERIOR POLIOMYELITIS IN THE CHICAGO AREA IN 1931; CLINICAL FACTORS AND SERUM THERAPY. DR. WILLIAM THALHIMER, DR. SIDNEY O. LEVINSON and CLARICE MCDOUGALL (by invitation).

The medical profession is most interested in knowing whether pooled convalescent poliomyelitis serum and pooled serum from normal adults has any value in the therapy in preparalytic poliomyelitis or in the paralytic stage of the disease.

At this point, it is only fair to state that the enthusiasm of some of the first investigators has given way to doubt. It is our impression, however, that these serums were of definite aid in some of the cases which came under our observation. We can give you our reasons for this belief, which is based on our personal experience in individual patients who received serum. Deductions from clinical observations even in individual cases, we believe, contribute important evidence in the evaluation of therapeutic measures, and must be considered of equal importance with statistical studies. We have no desire to force the issue in favor of serum and have tried to keep an open mind about its value. We merely wish to ask you at this time similarly to keep an open mind, especially in view of the recent statistical reports concerning serum therapy in poliomyelitis. We do not believe that the question has been settled yet, and it is only by remaining unprejudiced that we may all contribute in the future toward the solution of this problem.

An analysis was made of the statistical report of recent papers by Kramer, by Park and by Laidlaw. The discrepancy between the mortality rate for untreated preparalytic patients, in whom the condition progressed to paralysis, and the mortality rate of other patients, who were paralyzed when first seen, is difficult to account for. These valuable contributions do not seem to solve the problem of the therapeutic value of convalescent poliomyelitis serum. The statistics in our report also are difficult to evaluate.

Even with the best statistical methods, we seem rather to increase the number of unanswerable problems than to diminish them. Can it be that accidentally all of the patients who are observed everywhere in the preparalytic stage, whether treated with serum or not, have mild cases showing a low mortality and depriving us of the possibility of ever evaluating the therapeutic use of serum? If so, all the patients seen in the paralytic stage are victims of the most severe form of the disease.

In the desire to do everything possible for these patients, one must not lose sight of the danger of classifying some who are already in the early paralytic stage as preparalytic patients. In fact, one must consider the possibility that in our anxiety about this disease some cases are diagnosed as preparalytic poliomyelitis which are not.

In this quandry some of us believe, as has been pointed out by Shaw and his co-workers, that when patients are treated with serum, clinical observations made

by physicians with a comprehensive background and first hand knowledge of the disease may yield evidence of more value than that arrived at by the statistical route.

Finally, we believe that in spite of the earnest efforts made to date, the question must still remain open as to whether pooled convalescent serum and pooled serum of normal adults are of value in the treatment of poliomyelitis. We think that in spite of statistical reports we should all retain an open mind to this problem. Since we have gained the present impression that serum is of therapeutic value, we believe that the study of its use should continue. We think that controlled observations made by treatment in alternate cases should be carried out. Particular attention should be paid in the future to using larger amounts of serum, and by that is meant at least two or three times the amounts used at present. Since it would be impossible during an epidemic to secure this huge amount of convalescent serum, and since pooled normal adult serum has been shown in the laboratory to have the same power to neutralize the virus, it would be logical, as well as economical, to use large amounts of pooled normal adult serum, which could be collected with great ease and speed. In the absence of any other therapeutic hope, it would seem unwise to abandon serum therapy on the basis of the evidence gathered to date.

DISCUSSION OF PAPERS ON POLIOMYELITIS

DR. CLIFFORD G. GRULEE: I have learned a great deal from these papers. I wish to ask Dr. Hunt and Dr. Thalhimer what are the criteria on which a diagnosis of preparalytic poliomyelitis has been made.

I ask that because recently in one of the suburbs of this city there appeared in the health bulletin a report of thirty cases of poliomyelitis of the nonparalytic type in which not a single case of paralysis was found. It seems to me that one should be certain when one makes a diagnosis of poliomyelitis before one tells any one about it. I am persuaded that many cases of sore throat with stiff neck are diagnosed as poliomyelitis, and I should like to have this impressed on the younger members of the society by those who know just what the criteria are so that such mistakes cannot occur in the future.

DR. JOSEPH BRENNEMANN: I think that the crux of the whole situation lies in the difficulty of making a diagnosis of poliomyelitis in the preparalytic stage, except during an epidemic, and in the utter inability to prognosticate with any degree of accuracy the outcome in any given case with or without any given treatment. Both of these factors certainly preclude the possibility of making dependable deductions as to treatment, because control is practically impossible. From all of the recent publications, it is evident that statistics can appear either way, and that ultimately one must perhaps depend more on impressions than on statistics.

Dr. Thalhimer has given us a cleancut, frank and conservative presentation. There is one matter, however, which it seems to me should be brought into relief and which has not been discussed. There are two methods of giving convalescent serum, intraspinally and intramuscularly or intravenously. It is logical in the light of what we know about other immune serums to give convalescent serum intramuscularly with the hope of increasing the immunity of the patient. Intraspinal injections, on the other hand, raise a different question. Again statistics are of little value, and one is perhaps justified in replying on impressions. My own impression has been that the injection of convalescent serum into the spine has not only done no good, but that it has possibly done some harm.

DR. FREDERIC W. SCHLUTZ: In connection with the discussion of Dr. Grulee and Dr. Brennemann, I am reminded of an experience we had in Minnesota some years ago. There was a severe epidemic of poliomyelitis in Minneapolis at the time. Dr. Rosenow of the Mayo Clinic was enthusiastic about a serum which he had developed for this disease. He saw a number of cases, mostly in Iowa, and seemed to get these patients in the preparalytic stage. The effect of the

serum seemed to be favorable, but, as I remember, it was not so successful in the cases in which the condition had gone on to the paralytic stage. I was struck at the time with the fact that it was exceedingly difficult for us to diagnose poliomyelitis in the preparalytic stage. It may have been due to inadequate technic, but it surely seemed to be difficult to establish such a diagnosis. I believe that one must be very careful in making such a diagnosis, and there must be every available and possible proof of the condition.

Some time ago Dr. Rosenow developed a precipitin test which he considered of great value in making an early diagnosis of poliomyelitis. Personally, I have had little experience with this test. I should like to ask Dr. Thalhimer whether it is still being used and whether it is of any value.

Dr. Hunt mentioned an item in the treatment of poliomyelitis which I wish to endorse heartily. It is the complete immobilization of the patient. The late Dr. Allison insisted that this be done at the earliest moment possible, and that the child be immobilized in a cast and kept in that state of immobilization for several weeks. He felt that this measure was one of the best possible ways to prevent serious progress of the disease.

DR. MAXWELL P. BOROVSKY: I was much interested in poliomyelitis in the Negro, and wish to call attention to the fact that, aside from its being uncommon in the Negro, it seems to select a particular type in the white race, and that is the good looking, well developed blond. This has been noticed by many physicians and seems to be borne out by our clinical experience. There was one occasion when he had several cases in the hospital in which the degree of involvement was almost comparable to the complexion of the patient, the pale, waxen-skinned and blond haired patients having the most severe infection. This does not mean that poliomyelitis may not occur in the brunette, but this point is important to bear in mind, and an effort should be made to get some clinical explanation for it.

DR. HENRY E. IRISH: I should like to know whether, in connection with the pooled serum, either of the essayists has any knowledge that would seem to indicate that the serum of patients recently afflicted, that is, in whom the onset occurred six months previously or more, is any more potent in neutralizing the virus than that of patients who have been afflicted for a longer period.

DR. ARCHIBALD HOYNE: There seems to be no doubt that considerable confusion of ideas exists in regard to this disease. If one looks back to 1905, one finds that Wickmann observed instances of poliomyelitis in which paralysis did not occur. He classed cases of this kind as abortive. However, in recent years, we have been told that as many as 85 per cent of all patients with poliomyelitis have no paralysis. If 85 per cent have no paralysis, it seems questionable whether the term "preparalytic stage" should have such constant usage. Moreover, for similar reasons one finds that the term abortive is commonly regarded as obsolete at present.

By some, poliomyelitis has been defined as an acute infectious systemic disease in which paralysis may occur, though not usually. In other words, paralysis in poliomyelitis is frequently regarded as a complication of the disease rather than as one of its constant symptoms. Because of the foregoing assertions, is it proper to claim that the application of any special treatment prevents paralysis in cases in which no paralysis develops?

The situation in respect to the fatality rate seems to be no different now from what it was in 1917. In other words, it is the type of the disease and not the form of treatment that determines the rate of mortality. We know that there is no reason to expect a fatal termination in a case of poliomyelitis merely because a group of muscles or one or more extremities are paralyzed. On the other hand, in a patient with the respiratory type of the disease, recovery is most unusual. In addition, it has been recorded in some epidemics that as many as 50 per cent of all of the patients have made a complete recovery.

Because of the natural tendency toward improvement in nonfatal cases, varied conclusions may be drawn in respect to any special treatment that has been adopted. The following instance is an excellent illustration of this fact.

At the Cook County Contagious Disease Hospital we had been using some blood from the parents of patients in the treatment of poliomyelitis on the theory that such blood might contain neutralizing bodies that would be of value in the treatment of patients. In a nearby city there was a case of poliomyelitis, and a telephone call was received by the County Hospital requesting information concerning our methods of treating poliomyelitis. An intern conveyed the information over the telephone that we had been using parents' blood. Through a misunderstanding of the conversation the physician secured a parrot, after much difficulty, from which he obtained 5 cc. of blood and injected this into the patient with poliomyelitis. Nevertheless, although parrot's blood instead of parents' blood was given, the treatment was reported as successful.

Notwithstanding any possible doubts concerning the true value of serum therapy, I believe that it would be a great mistake to deprive a patient with poliomyelitis of this treatment, provided convalescent serum is available.

DR. LUKE W. HUNT: Answering Dr. Grulee's question, Dr. Gordon of Detroit says the best way to diagnose the condition in preparalytic cases is to have a healthy clinical suspicion of the disease and to perform a lumbar puncture. Often we are doubtful as to its presence. In one case a child had a high fever and a sore throat but no other evidence of poliomyelitis, and the spinal fluid changes were typical of the disease. We found out later that the boy had been hit on the head with a basket ball the day before. Whether that injury was sufficient to produce the changes in the spinal fluid is problematic. We have to make the diagnosis on the basis of the clinical picture, the physical findings and the tests of the spinal fluid. All of those are subject to error or to misinterpretation, and in some cases doubt may exist if no paralysis develops.

As to comments of Dr. Borovsky, I do not know of any explanation for the occurrence of poliomyelitis in the type of person described. In his book Dr. Draper mentioned some of the characteristics, but offered no explanation, and I have none.

DR. WILLIAM THALHIMER: In the time at our disposal, we could not touch on the amount of serum to be used or on many other factors that interest us. We believe that the minimum amount of serum used in a case should be 80 cc. This is usually given, 20 cc. being injected into the spinal canal and the other 60 cc. by whatever route is preferred. We believe that in the future it is important to use larger amounts of serum to determine whether or not more benefit is conferred by these larger doses.

Dr. Brennemann's question of the wisdom of using serum intraspinally is a legitimate one. We have seen no unfavorable results, except a temporary increase in headache, rigidity and tenderness of the spine. Since there is already evidence of an inflammatory reaction in the spinal fluid, which indicates that the meningeal barrier has already been interrupted, we do not believe that any breakdown in this barrier is caused by the injection of a material as bland as human serum. In fact, in six cases in which there was occasion to perform lumbar punctures from eighteen to forty-eight hours after an intrathecal injection of human serum, there was a reduction of the cells in the spinal fluid in two instances, a mild increase in three and a definite increase in one. The inflammatory reaction was much less than would have followed the injection of an animal serum intrathecally.

No information that we know of indicates that serum obtained soon after an attack of poliomyelitis is more potent than serum obtained after a long interval. In fact, it is not known how soon after the attack the neutralizing substance is found in the patient's blood.

It might be perfectly proper for Dr. Hoyne to question the accuracy of the diagnosis of preparalytic poliomyelitis in some instances, even though the spinal fluid shows an increase in globulin and leukocytes. These changes and the clinical picture together definitely indicate the presence of an infectious disease and inflammation of the meninges. This seems to me sufficient evidence to indicate the presence of an infectious disease involving the central nervous system which must be called either poliomyelitis or encephalomyelitis, unless these conditions can be proved to be due to some other disease.

Book Reviews

Die Nervenkrankheiten des Kindesalters. By Prof. Dr. George Peritz. Second edition. Price, 39.50 marks. Pp. 664. Leipzig: Fischers medicinische Buchhandlung, 1932.

The second edition of this good textbook on diseases of the nervous system in children has been fully revised and brought up to date. It is extremely complete in all its details and has taken note of various contributions, especially to the German literature. Few references to literature other than the German are to be found.

On the whole, the book is a complete one on neurology and takes up in detail all the neurologic conditions that may affect children. The first part of the book is devoted to general subjects; the second part takes up the special diseases, starting with the cerebral palsies, then hereditary diseases of the nervous system, tumors and inflammation. There is an excellent chapter on diseases of the internal secretions and how they affect the nervous system, and also one on tetany. An interesting portion of this chapter is given to infantilism; neurosis and psychosis are discussed thoroughly.

The book is nicely prepared, and is well though not profusely illustrated.

Le rachitisme et la tétanie. By Edmond Lesné and Lucien de Gennes. Paper. Price, 30 francs. Pp. 140, with 31 plates. Paris: Gauthier-Villars & Cie, 1932.

The first ninety-one pages of this book are devoted to rickets. The various chapters deal with the history, clinical forms, differential diagnosis, etiology, pathology and treatment. These subjects are covered in a brief but thorough manner. The chapter on treatment is interesting because of its conservatism. Prophylactic treatment consists in merely fresh air, sunshine and cod liver oil. The curative treatment is first ultraviolet rays and second cod liver oil. The authors believe that with a potent oil a teaspoonful dose a day is sufficient. Irradiated products are given a third place, with a warning that it is a grave error to confound irradiated products with cod liver oil. It is refreshing to note that these authors, at least, have not been stampeded by propaganda into using this form of therapy. Tetany is taken up in practically the same manner as rickets. Treatment with parathyroid extract, calcium salts, ammonium chloride, light and irradiated products is well discussed. Thirty-one excellent plates are appended, showing rachitic changes in the bones and histologic studies.

Public Health Reports. By United States Public Health Service. Volume 47. Pp. 1469. July 8, 1932.

For the period from May 22 to June 18, 1932, typhoid fever rose in its usual seasonal incidence, particularly in the East North Central, South Central and Mountain and Pacific Group. Poliomyelitis also rose in all sections, although still being 13 per cent below the corresponding time of last year. Measles also shows an increase, there being 63,506 cases reported. This rise was particularly in the East North Central States.

Smallpox, scarlet fever, influenza, diphtheria and meningitis all show a decrease.

The average mortality rate was 10.7 per thousand. This is the lowest mortality rate reported in the last seven years for which records are available.

Children and Parents. By Maud E. Watson, Ph.D. Price, $3.50. Pp. 362. New York: F. S. Crafts & Company, 1932.

This extremely interesting book is made up largely of the discussion of nine children presenting behavior problems. There is also a general discussion of the technic of history taking and treatment.

The outstanding factor of the presentation is the elaborate but essential history taking. Not only the facts but also their interpretation and effect on the behavior of the patient are given. The attitude assumed is psychoanalytic. The psychoanalysis and plans of treatment are not so well presented.

The book is well written and interesting throughout. It provides profitable reading for any one dealing with children.

The Sputum. By Randall Clifford, M.D. Price, $4. Pp. 167, with 21 figures and 8 plates. New York: The Macmillan Company, 1932.

This book contains general observations on the sputum — macroscopic examination and chemical examination. The microscopic examination details the Ziehl-Neelsen stain, Smith's gram-eosin stain, with the various organisms found in it, and the Fontanna stain for spirochetes. The final section discusses the character and clinical significance of the sputum in some of the more common diseases of the bronchi and lungs. The book is well printed, and the plates and figures are excellent. The subject matter is discussed in a concise and readable manner.

Directory of Pediatric Societies

INTERNATIONAL

International Association of Preventive Pediatrics

President: Professor Taillens, Lausanne, Switzerland.
Secretary: Dr. P. Oltramare, rue Decandolle, Geneva, Switzerland.

International Pediatric Congress

President: Dr. George Frederic Still, 28 Queen Anne St., London, W. 1.
Secretary: Dr. Leonard K. Findlay, 61 Harley St., London, W. 1.
Place: London. Time: July 20-23, 1933.

FOREIGN

Royal Society of Medicine, Section for the Study of Disease in Children

President: Dr. Leonard G. Parsons, 58, Calthorpe Road, Birmingham, England.
Secretary: Dr. W. G. Wyllie, 33, Wimpole St., W. 1, London.
Place: London. Time: May 26, 1933.

NATIONAL

American Medical Association, Scientific Assembly, Section on Diseases of Children

Chairman: Dr. Frederic W. Schlutz, Bobs Roberts Hospital, University of Chicago, Chicago.
Secretary: Dr. Alfred A. Walker, Highland Plaza Apartments, Birmingham, Ala.
Place: Milwaukee. Time: June 12-16, 1933.

American Academy of Pediatrics

President: Dr. Samuel McC. Hamill, 1822 Spruce St., Philadelphia.
Secretary: Dr. C. G. Grulee, 636 Church St., Evanston, Ill.

American Child Health Association

President: Dr. Samuel McC. Hamill, 1822 Spruce St., Philadelphia.
Secretary: Dr. Philip Van Ingen, 125 E. 71st St., New York.

American Hospital Association, Section on Children's Hospitals

President: Dr. Thomas B. Cooley, 7815 E. Jefferson Ave., Detroit.
Secretary: Miss Bena M. Henderson, 721 N. 17th St., Milwaukee.

American Pediatric Society

President: Dr. Oscar M. Schloss, 1185 Park Ave., New York.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid, St. Louis.
Place: Washington, D. C. Time: May 8-10, 1933.

Association of American Teachers of the Diseases of Children

President: Dr. Ralph M. Tyson, 334 S. 21st St., Philadelphia.
Secretary: Dr. Oscar Reiss, 1930 Wilshire Blvd., Los Angeles.

Canadian Society for the Study of Diseases of Children

President: Dr. Frederick F. Tisdall, 170 St. George St., Toronto, Ontario.
Secretary-Treasurer: Dr. T. G. H. Drake, 67 College St., Toronto, Ontario.

Society of Pediatric Research

President: Dr. Bengt Hamilton, University of Chicago, Chicago.
Secretary-Treasurer: Dr. Charles F. McKhann, Harvard Medical School, Boston.
Place: New York. Time: May 6, 1933.

SECTIONAL

Central States Pediatric Society

President: Dr. Frank C. Neff, 406 W. 34th St., Kansas City, Mo.
Secretary: Dr. A. H. Parmelee, 715 Lake St., Oak Park, Ill.

North Pacific Pediatric Society

President: Dr. Herbert E. Coe, 509 Olive St., Seattle.
Secretary: Dr. Raymond H. Somers, Cobb Bldg., Seattle.
Place: Seattle. Time: Jan. 28, 1933.

Southern Medical Association, Section on Pediatrics

Chairman: Dr. Horton Casparis, Vanderbilt University Hospital, Nashville, Tenn.
Secretary: Dr. Luther W. Holloway, 117 W. Duval St., Jacksonville, Fla.

STATE

Alabama Pediatric Society

President: Dr. Thomas J. McElhenney, 1722, 2nd Ave., Bessemer.
Secretary-Treasurer: Dr. John W. Simpson, 1117 S. 22d St., Birmingham.

Georgia Pediatric Society

President: Dr. M. Hines Roberts, Atlanta.
Secretary-Treasurer: Dr. Roger W. Dickson, 33 Ponce de Leon Ave., N. E., Atlanta.

Louisiana State Pediatric Society

President: Dr. Cecil O. Lorio, 245, 3d St., Baton Rouge.
Secretary-Treasurer: Dr. Maud Loeber, 3503 Prytania St., New Orleans.

Medical Society of State of New York

Chairman: Dr. Brewster Doust, 605 Medical Arts Bldg., Syracuse.
Secretary: Dr. G. C. Sincerbeaux, 6 William St., Auburn.

Nebraska Pediatric Society

President: Dr. W. O. Colburn, 724 Sharp Bldg., Lincoln.
Secretary-Treasurer: Dr. C. G. Weigand, 1614 Medical Arts Bldg., Omaha.
Place: As announced by committee. Time: Second Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

North Carolina Pediatric Society

President: Dr. Yates W. Faison, 121 W. 7th St., Charlotte.
Secretary: Dr. E. K. McLean, 121 W. 7th St., Charlotte.
Place: Various children's hospitals. Time: Twice a year.

Oklahoma State Pediatric Society

President: Dr. Clark H. Hall, 117 N. Broadway, Oklahoma City.
Secretary: Dr. M. J. Searle, 108 W. 6th St., Tulsa.

South Carolina Pediatric Society

President: Dr. T. D. Dotterer, 1512 Marion, Columbia.
Secretary-Treasurer: Dr. Julian P. Price, 117 W. Cheves St., Florence.

Texas Pediatric Society

President: Dr. Boyd Reading, 2201 Avenue D, Galveston.
Secretary-Treasurer: Dr. F. W. Hoehn, 1006 Medical Arts Bldg., Waco.

Virginia Pediatric Society

President: Dr. St. Geo. Grinnan, 925 W. Grace St., Richmond.
Secretary-Treasurer: Dr. J. B. Stone, 2042 Park Ave., Richmond.

West Virginia State Medical Society, Section on Pediatrics

President: Dr. George M. Lyon, 955, 4th Ave., Huntington.
Secretary: Dr. M. F. Petersen, 1013 Quarrier St., Charleston.

LOCAL

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. J. E. McClelland, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. P. G. Albrecht, 2009 Adelbert Rd., Cleveland.
Place: 2009 Adelbert Road. Time: Four meetings, from September to May.

Academy of Medicine, Toronto, Section of Pediatrics

Secretary: Dr. Lawrence Murray, 1870 Bloor St., W., Toronto.
President: Dr. Gladys Boyd, 56 DeLisle St., Toronto.

Bronx Pediatric Society

President: Dr. Henry M. Eisenoff, 1018 E. 163rd St., New York.
Secretary: Dr. Morris Gleich, 9 Post Ave., New York.
Place: Concourse Plaza, 161st St. and Grand Concourse. Time: Second Wednesday of each month, except June, July, August and September.

Brooklyn Pediatric Society

President: Dr. Irwin Schiff, 658 Eastern Parkway, Brooklyn.
Secretary: Dr. Louis A. Koch, 62 Pierrepont St., Brooklyn.
Place: Kings County Medical Society Bldg. Time: Last Wednesday of each month, except June, July and August.

Central New York Pediatric Club

President: Dr. Frank Vander Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various cities in New York. Time: Fourth Thursday of October, January and April.

Chicago Pediatric Society

President: Dr. Archibald L. Hoyne, 25 E. Washington St., Chicago.
Secretary: Dr. Bert I. Beverly, 8 S. Michigan Ave., Chicago.
Place: City Club. Time: Third Tuesday of each month.

Dallas County Pediatric Society

President: Dr. Gordon B. McFarland, Medical Arts Bldg., Dallas, Texas.
Secretary: Dr. Harold T. Nesbit, Medical Arts Bldg., Dallas, Texas.
Place: Bradford Memorial Hospital. Time: 1 p. m., first and third Saturdays of each month.

Detroit Pediatric Society

President: Dr. Bernard Bernbaum, 5057 Woodward Ave. Detroit.
Secretary: Dr. Sarah S. Schooten, 5057 Woodward Ave., Detroit.
Place: Children's Hospital of Michigan. Time: No fixed date; approximately once a month.

Fulton County Medical Society, Pediatric Section (Atlanta, Ga.)

Chairman: Dr. T. Bolling Gay, 384 Peachtree St., Atlanta.
Secretary: Dr. Roger W. Dickson, 33 Ponce de Leon Ave., N. E., Atlanta.
Place: Academy of Medicine, 32 Howard St. Time: Second Thursday of each month from October to April, 8 p. m.

Memphis Pediatric Society

President: Dr. William R. Graves, 1193 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Harry J. Jacobson, 1193 Madison Ave., Memphis, Tenn.
Place: Memphis General Hospital. Time: Second Tuesday of each month.

Milwaukee Pediatric Society

President: Dr. G. H. Fellman, 231 W. Wisconsin Ave., Milwaukee.
Secretary: Dr. George F. Kelly, 161 W. Wisconsin Ave., Milwaukee.
Place: Children's Hospital. Time: Second Wednesday of each alternate month, beginning with February.

New England Pediatric Society

President: Dr. Lewis Webb Hill, 319 Longwood Ave., Boston.
Secretary: Dr. Gerald Hoeffel, 319 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

New York Academy of Medicine, Section of Pediatrics

Chairman: Dr John Caffey, 50 Haven Ave., New York.
Secretary: Dr. Harry Bakwin, 132 E. 71st St., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

Northern California Pediatric Society

President: Dr. Edward B. Shaw, 384 Post St., San Francisco.
Secretary-Treasurer: Dr. Lloyd Hardgrave, 384 Post St., San Francisco.
Place: Various teaching schools. Time: Monthly.

Northwestern Pediatric Society

President: Dr. Irving McQuarrie, Dept. Pediatrics, University of Minnesota, Minneapolis.
Secretary: Dr. Alexander Stewart, 459 Lowry Medical Arts Bldg., St. Paul.

Philadelphia Pediatric Society

President: Dr. John P. Scott, 2040 Pine St., Philadelphia.
Secretary: Dr. John D. Donnelly, 115 Bryn Mawr Ave., Bala-Cynwyd, Pa.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday of each month from October to June, inclusive.

Pittsburgh Pediatric Society

President: Dr. Henry C. Flood, 119 S. Highland Ave., Pittsburgh.
Secretary: Dr. E. R. McCluskey, Highland Bldg., Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate months from October to April, inclusive.

Richmond Pediatric Society

President: Dr. John S. Weitzel, 3103 W. Franklin St., Richmond, Va.
Secretary-Treasurer: Dr. W. E. Chapin, 922 Floyd Ave., Richmond, Va.
Place: Retreat for the Sick, 2621 Grove Ave. Time: First Thursday of each month (other than during the summer).

Rochester Pediatric Society

President: Dr. S. W. Clausen, Strong Memorial Hospital, Rochester, N. Y.
Secretary: Dr. F. W. Bush, 29 N. Goodman St., Rochester, N. Y.
Place: Arranged by program committee. Time: Second Friday of each month from October to May.

Rocky Mountain Pediatric Society

President: Dr. C. H. Platz, Fort Collins, Colo.
Secretary: Dr. R. H. Verploeg, 1850 Gilpin St., Denver.
Place: Children's Hospital, Denver. Time: Third Saturday of each month from September to May, inclusive, 2:30 p. m.

St. Louis Pediatric Society

President: Dr. Hugh McCulloch, 325 N. Euclid Ave., St. Louis.
Secretary-Treasurer: Dr. Katherine Bain, Beaumont Bldg., St. Louis.
Place: St. Louis Medical Society. Time: Third Friday of every month.

Seattle Pediatric Society

President: Dr. C. L. Smith, 1215, 4th Ave., Seattle.
Secretary: Dr. N. W. Murphy, 515 Cobb Bldg., Seattle.
Place: College Club. Time: Third Friday of each month, 7 p. m.

Southwestern Pediatric Society

President: Dr. Donald K. Woods, 2545 4th Ave., San Diego, Calif.
Secretary: Dr. Jeanette Harrison, 1136 W. 6th St., Los Angeles.
Place: University Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Henry G. Poncher, 5325 Kenmore Ave., Chicago.
Secretary: Dr. John P. Parsons, 320 S. Division St., Ann Arbor, Mich.

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